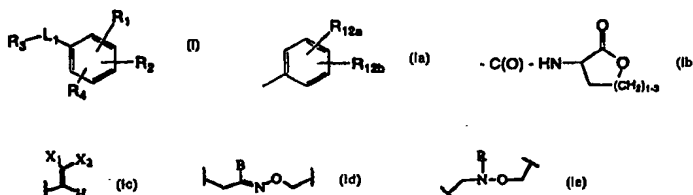




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/38, 31/39, 31/40, 31/415, 31/42, 31/425, 31/44, 31/445, 31/495, 31/505, 31/095, 31/18, C07D 207/09, 233/54, 239/24, 241/04, 263/02, 277/28, 307/00, 333/00, 209/10, C07C 303/00, 307/00, 309/00, 313/00	A1	(11) International Publication Number: WO 98/50030 (43) International Publication Date: 12 November 1998 (12.11.98)
(21) International Application Number: PCT/US98/09297 (22) International Filing Date: 7 May 1998 (07.05.98) (30) Priority Data: 08/852,858 7 May 1997 (07.05.97) US (71) Applicant: UNIVERSITY OF PITTSBURGH [US/US]; Office of Technology Transfer, 911 Williams Pitt Union, Pittsburgh, PA 15260 (US). (72) Inventors: SEBTI, Said, M.; 8957 Magnolia Chase Circle, Tampa, FL 33647 (US). HAMILTON, Andrew, D.; 1 White Pine Lane, Guilford, CT 06437 (US). AUGERI, David, J.; 6846 3rd Avenue, Kenosha, WI 53143 (US). BARR, Kenneth, J.; 4828 N. Hermitage #3A, Chicago, IL 60640-4143 (US). DONNER, Bernard, G.; 1901 McRae Lane, Mundelein, IL 60060 (US). FAKHOURY, Stephen, A.; 517 Buckingham, Mundelein, IL 60060 (US). JANOWICK, David, A.; 37070 Ganster Road, Beach Park, IL 60087 (US). KALVIN, Douglas, M.; 1201 Lockwood Drive, Buffalo Grove, IL 60069 (US). LARSEN,		John, J.; 10542 Altegld Street, Melrose Park, IL 60164 (US). LIU, Gang; 838 Alderly Lane, Gurnee, IL 60031 (US). O'CONNOR, Stephen, J.; 2103 Washington Avenue, Wilmette, IL 60091 (US). ROSENBERG, Saul, H.; 15 Lighthouse Lane, Grayslake, IL 60030 (US). SHEN, Wang; 6215 Formoor Lane, Gurnee, IL 60031 (US). SWENSON, Rolf, E.; 285 Penny Lane, Grayslake, IL 60030 (US). SORESENSEN, Bryan, K.; 2620 North Lewis Avenue, Waukegan, IL 60087 (US). SULLIVAN, Gerard, M.; 2214 North Sunrise Drive, Round Lake Beach, IL 60073 (US). SZCZEPANKIEWICZ, Bruce, G.; 33720 Royal Oake Lane, Apt. 209, Gages Lake, IL 60030 (US). TASKER, Andrew, S.; 6251 Eagle Ridge Drive, Gurnee, IL 60031 (US). WASICK, James, T.; 28440 Dorie Lane, Waterford, WI 53185 (US). WINN, Martin; 1263 Carlisle Place, Deerfield, IL 60015 (US). (74) Agents: KOKULIS, Paul, N. et al.; Cushman Darby & Cushman, Intellectual Property Group of Pillsbury Madison & Sutro, 1100 New York Avenue, N.W., Washington, DC 20005 (US). (81) Designated States: CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES



(57) Abstract

Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein R_1 is (a) hydrogen, (b) loweralkyl, (c) alkenyl, (d) alkoxy, (e) thioalkoxy, (f) halo, (g) haloalkyl, (h) aryl- L_2 -, and (i) heterocyclic- L_2 -; R_2 is selected from (a) (Ia), (b) $-C(O)NH-CH(R_{14})-C(O)OR_{15}$, (c) (Ib), (d) $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$, (e) $-C(O)NH-CH(R_{14})$ -tetrazolyl, (f) $-C(O)NH$ -heterocyclic, and (g) $-C(O)NH-CH(R_{14})-C(O)NR_{17}R_{18}$; R_3 is substituted or unsubstituted heterocyclic or aryl, substituted or unsubstituted cycloalkyl or cycloalkenyl, (Ic), and $-P(W)R^3R^3R^3$; R_4 is hydrogen, lower alkyl, haloalkyl, halogen, aryl, arylalkyl, heterocyclic, or (heterocyclic)alkyl; L_1 is absent or is selected from (a) $-L_4-N(R_5)-L_5$ -, (b) $-L_4-O-L_5$ -, (c) $-L_4-S(O)_n-L_5$ -, (d) $-L_4-L_6-C(W)-N(R_5)-L_5$ -, (e) $-L_4-L_6-S(O)_m-N(R_5)-L_5$ -, (f) $-L_4-N(R_5)-C(W)-L_7-L_5$ -, (g) $-L_4-N(R_5)-S(O)_p-L_7-L_5$ -, (h) optionally substituted alkylene, (i) optionally substituted alkenylene, (j) optionally substituted alkynylene, (k) a covalent bond, (l) (Id), and (m) (Ie) are inhibitors of protein isoprenyl transferases. Also disclosed are protein isoprenyl transferase inhibiting compositions and a method of inhibiting protein isoprenyl transferases.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES

Technical Field

10 The present invention relates to novel compounds which are useful in inhibiting protein isoprenyl transferases (for example, protein farnesyltransferase and protein geranylgeranyltransferase) and the farnesylation or geranylgeranylation of the oncogene protein Ras and other related small g-proteins, compositions containing such compounds and methods of using such compounds.

Background of the Invention

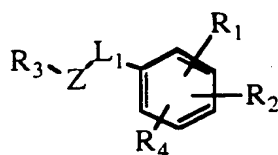
15 Ras oncogenes are the most frequently identified activated oncogenes in human tumors. Transformed protein Ras is involved in the proliferation of cancer cells. The Ras must be farnesylated before this proliferation can occur. Farnesylation of Ras by farnesyl pyrophosphate (FPP) is effected by protein farnesyltransferase. Inhibition of protein farnesyltransferase, and thereby farnesylation of the Ras protein, blocks the ability of transformed cells to proliferate. Inhibition of protein geranylgeranyltransferase and, thereby, of geranylgeranylation of Ras proteins, also results in down regulation of Ras protein function.

25 Activation of Ras and other related small g-proteins that are farnesylated and/or geranylated also partially mediates smooth muscle cell proliferation (Circulation, 1-3: 88 (1993), which is hereby incorporated herein by reference). Inhibition of protein isoprenyl transferases, and thereby farnesylation or geranylgeranylation of the Ras protein, also aids in the prevention of intimal hyperplasia associated with restenosis and atherosclerosis, a condition which compromises the success of angioplasty and surgical bypass for obstructive vascular lesions.

30 There is therefore a need for compounds which are inhibitors of protein farnesyltransferase and protein geranylgeranyltransferase.

Summary of the Invention

35 In its principle embodiment, the invention provides a compound having the formula:



I

or a pharmaceutically acceptable salt thereof, wherein

R₁ is selected from the group consisting of

- (1) hydrogen,
- (2) alkenyl,
- (3) alkynyl,
- (4) alkoxy,
- 45 (5) haloalkyl,
- (6) halogen,
- (7) loweralkyl,
- (8) thioalkoxy,
- (9) aryl-L₂- wherein aryl is selected from the group consisting of

- 50 (a) phenyl,
- (b) naphthyl,
- (c) dihydronaphthyl,
- (d) tetrahydronaphthyl,
- (e) indanyl, and
- 55 (f) indenyl

wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y,
or Z wherein X, Y, and Z are independently selected from the
group consisting of

- 60 alkenyl,
- alkynyl,
- alkoxy,
- aryl,
- carboxy,
- cyano,
- 65 halogen,
- haloalkyl,
- hydroxy,
- hydroxyalkyl,
- loweralkyl,
- 70 nitro,

N-protected amino, and

-NRR' wherein R and R' are independently selected

from the group consisting of

hydrogen and

loweralkyl,

oxo (=O), and

thioalkoxy and

L₂ is absent or is selected from the group consisting of

-CH₂-,

-CH₂CH₂-,

-CH(CH₃)-,

-O-,

-C(O)-,

-S(O)_q wherein q is 0, 1 or 2, and

-N(R)-, and

(10) heterocycle-L₂- wherein L₂ is as defined above and the heterocycle is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

(a) loweralkyl,

(b) hydroxy,

(c) hydroxyalkyl,

(d) halogen

(e) cyano,

(f) nitro,

(g) oxo (=O),

(h) -NRR',

(i) N-protected amino,

(j) alkoxy,

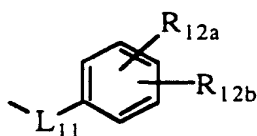
(k) thioalkoxy,

(l) haloalkyl,

(m) carboxy, and

(n) aryl;

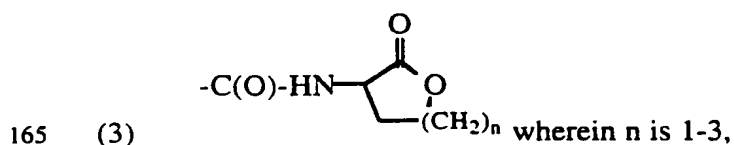
R₂ is selected from the group consisting of



- 105 (1) wherein L_{11} is selected from the group consisting of
- (a) a covalent bond,
 - (b) $-C(W)N(R)-$ wherein R is defined previously and W is selected from the group consisting of O and S ,
 - 110 (c) $-C(O)-$,
 - (d) $-N(R)C(W)-$,
 - (e) $-CH_2O-$,
 - (f) $-C(O)O-$, and
 - (g) $-CH_2N(R)-$,
 - 115 R_{12a} is selected from the group consisting of
 - (a) hydrogen,
 - (b) loweralkyl, and
 - (c) $-C(O)OR_{13}$ wherein R_{13} is selected from the group consisting of
 - 120 hydrogen and
 - a carboxy-protecting group, and
 - R_{12b} is selected from the group consisting of
 - (a) hydrogen and
 - (b) loweralkyl,
 - 125 with the proviso that R_{12a} and R_{12b} are not both hydrogen,

- (2) $-L_{11}-C(R_{14})(R_v)-C(O)OR_{15}$ wherein L_{11} is defined previously,
- R_v is selected from the group consisting of
- (a) hydrogen and
 - 130 (b) loweralkyl,
- R_{15} is selected from the group consisting of
- (a) hydrogen,
 - (b) alkanoyloxyalkyl,
 - (c) loweralkyl, and
 - 135 (b) a carboxy-protecting group, and
- R_{14} is selected from the group consisting of
- (a) alkoxyalkyl,
 - (b) alkoxyarylalkyl,

- 140 (c) alkoxycarbonylalkyl,
 (d) alkylsulfinylalkyl,
 (e) alkylsulfonylalkyl,
 (f) alkynyl,
 (g) aminoalkyl,
 (h) aminocarbonylalkyl,
 145 (i) aminothiocabonylalkyl,
 (j) aryl,
 (k) arylalkyl,
 (l) carboxyalkyl,
 (m) cyanoalkyl,
 150 (n) cycloalkyl,
 (o) cycloalkylalkoxyalkyl,
 (p) cycloalkylalkyl,
 (q) (heterocyclic)alkyl,
 (r) hydroxyalkyl,
 155 (s) hydroxyarylalkyl,
 (t) loweralkyl,
 (u) sulfhydrylalkyl,
 (v) thioalkoxyalkyl wherein the thioalkoxyalkyl is
 unsubstituted or substituted with 1, 2, 3, or 4
 160 substituents selected from the group consisting of
 halogen,
 (w) thioalkoxyalkylamino, and
 (x) thiocycloalkyloxyalkyl,



- (4) $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$ wherein R_{14} is defined previously
 and R_{16} is selected from the group consisting of
 170 (a) loweralkyl,
 (b) haloalkyl,
 (c) aryl wherein the aryl is unsubstituted or substituted with
 1, 2, 3, 4, or 5 substituents independently
 selected from the group consisting of

175 loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
180 oxo (=O),
-NRR'
N-protected amino,
alkoxy,
thioalkoxy,
185 haloalkyl,
carboxy, and
aryl, and

(d) heterocycle wherein the heterocycle is unsubstituted or
substituted with substituents independently
190 selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
195 cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
200 alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl;

205 (5) -C(O)NH-CH(R₁₄)-tetrazolyl wherein the tetrazole ring is unsubstituted
or substituted with loweralkyl or haloalkyl,

(6) -L₁₁-heterocycle,
210

- (7) $-C(O)NH-CH(R_{14})-C(O)NR_{17}R_{18}$ wherein R_{14} is defined previously
and R_{17} and R_{18} are independently selected from the group
consisting of

- (a) hydrogen,
- (b) loweralkyl,
- (c) arylalkyl,
- (d) hydroxy, and
- (e) dialkylaminoalkyl,

215

- 220 (8) $-C(O)OR_{15}$, and

- (9) $-C(O)NH-CH(R_{14})$ -heterocycle wherein R_{14} is as previously defined
and the heterocycle is unsubstituted or substituted with
loweralkyl or haloalkyl;

225

L_1 is absent or is selected from the group consisting of

- (1) $-L_4-N(R_5)-L_5-$ wherein L_4 is absent or selected from the group
consisting of

- (a) C_1 -to- C_{10} -alkylene and
- (b) C_2 -to- C_{16} -alkenylene,

230

wherein the alkylene and alkenylene groups are unsubstituted or
substituted with 1, 2, 3 or 4 substituents independently
selected from the group consisting of

alkenyl,
alkenyloxy,
alkenyloxyalkyl,
alkenyl[S(O)_q]alkyl,
alkoxy,

235

alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or
substituted with 1 or 2 hydroxyl substituents,
with the proviso that no two hydroxyls are attached to the
same carbon,

240

alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1, 2, or 3
substituents independently selected from the
group consisting of
halogen and

245

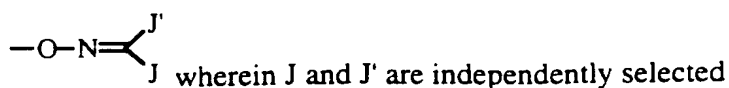
250 cycloalkyl,
 alkylsilyloxy,
 alkyl[S(O)_q],
 alkyl[S(O)_q]alkyl,
 aryl wherein the aryl is unsubstituted or substituted with
 1, 2, 3, 4, or 5 substituents independently
 selected from the group consisting of
255 alkoxy wherein the alkoxy is unsubstituted or
 substituted with substituents selected
 from the group consisting of cycloalkyl,
 aryl,
 arylalkyl,
260 aryloxy wherein the aryloxy is unsubstituted or
 substituted with 1, 2, 3, 4, or 5
 substituents independently selected from
 the group consisting of,
 halogen,
265 nitro, and
 -NRR',
 cycloalkyl,
 halogen,
 loweralkyl,
270 hydroxyl,
 nitro,
 -NRR', and
 -SO₂NRR',
 arylalkoxy wherein the arylalkoxy is unsubstituted or
275 substituted with substituents selected from the
 group consisting of alkoxy,
 arylalkyl,
 arylalkyl[S(O)_q]alkyl,
 aryl[S(O)_q],
280 aryl[S(O)_q]alkyl wherein the aryl[S(O)_q]alkyl is
 unsubstituted or substituted with 1, 2, 3, 4, or 5
 substituents independently selected from
 alkoxy and
 loweralkyl,

285 arylalkoxyalkyl wherein the arylalkoxyalkyl is
unsubstituted or substituted with substituents
selected from the group consisting of
alkoxy, and
halogen,
290 aryloxy,
aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or
substituted with substituents selected from the
group consisting of halogen,
carboxyl,
295 $-C(O)NR_C R_D$ wherein R_C and R_D are independently
selected from the group consisting of
hydrogen,
loweralkyl, and
alkoxycarbonyl or
300 R_C and R_D together with the nitrogen to which
they are attached form a ring selected
from the group consisting of
morpholine,
piperidine,
305 pyrrolidine
thiomorpholine,
thiomorpholine sulfone, and
thiomorpholine sulfoxide,
wherein the ring formed by R_C and R_D
310 together is unsubstituted or
substituted with 1 or 2
substituents independently
selected from the group consisting
of alkoxy and alkoxyalkyl,
315 cycloalkenyl wherein the cycloalkenyl is unsubstituted or
substituted with 1 or 2 substituents selected from
the group consisting of alkenyl,
cycloalkoxy,
cycloalkoxycarbonyl,
320 cycloalkoxyalkyl,
cycloalkyl wherein the cycloalkyl is unsubstituted or

substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting
of aryl,
325 loweralkyl, and
alkanoyl,
cycloalkylalkoxy,
cycloalkylalkoxycarbonyl,
cycloalkylalkoxyalkyl,
330 cycloalkylalkyl,
cycloalkyl[S(O)_q]alkyl,
cycloalkylalkyl[S(O)_q]alkyl,
fluorenyl,
heterocycle wherein the heterocycle is unsubstituted or
335 substituted with 1, 2, 3, or 4 substituents
independently selected from the group
consisting of
alkoxy wherein the alkoxy is unsubstituted or
substituted with 1 or 2 substituents
340 independently selected from the group
consisting of aryl and cycloalkyl,
alkoxyalkyl wherein the alkoxyalkyl is
unsubstituted or substituted with 1 or 2
substituents independently selected from
345 the group consisting of
aryl and
cycloalkyl,
alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1 or 2
350 substituents independently selected from
the group consisting of
aryl and
cycloalkyl,
aryl wherein the aryl is unsubstituted or
355 substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of
alkanoyl,

360 alkoxy,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
nitro,
365 -NRR', and
thioalkoxy,
arylalkyl,
aryloxy,
cycloalkoxyalkyl,
370 cycloalkyl,
cycloalkylalkyl,
halogen,
heterocycle,
hydroxyl,
375 loweralkyl wherein the loweralkyl is
unsubstituted or substituted with 1, 2, or
3 substituents independently selected
from the group consisting of
heterocycle,
380 hydroxyl,
with the proviso that no two hydroxyls
are attached to the same carbon,
and
-NR^{R3}R^{R3'} wherein R^{R3} and R^{R3'} are
385 independently selected from the
group consisting of
hydrogen
aryl,
loweralkyl,
390 aryl,
arylalkyl,
heterocycle,
(heterocyclic)alkyl,
cycloalkyl, and
395 cycloalkylalkyl, and

400 sulfhydryl,
 (heterocyclic)alkoxy,
 (heterocyclic)alkyl,
 (heterocyclic)alkyl[S(O)_q]alkyl,
 (heterocyclic)oxy,
 (heterocyclic)alkoxyalkyl,
 (heterocyclic)oxyalkyl,
 heterocycle[S(O)_q]alkyl,
 405 hydroxyl,
 hydroxyalkyl,
 imino,
 N-protected amino,
 =N-O-aryl, and
 =N-OH,
 410 =N-O-heterocycle wherein the heterocycle is
 unsubstituted or substituted with 1, 2, 3, or 4
 substituents independently selected from the
 group consisting of
 415 loweralkyl,
 hydroxy,
 hydroxyalkyl,
 halogen,
 cyano,
 nitro,
 420 oxo (=O),
 -NRR'
 N-protected amino,
 alkoxy,
 thioalkoxy,
 425 haloalkyl,
 carboxy, and
 aryl,
 =N-O-loweralkyl,
 -NRR³RR^{3'},
 430 -NHNR_CR_D,
 -OG wherein G is a hydroxyl protecting group,
 -O-NH-R,



from the group consisting of

loweralkyl and

arylalkyl,

oxo,

oxyamino(alkyl)carbonylalkyl,

oxyamino(arylalkyl)carbonylalkyl,

oxyaminocarbonylalkyl,

-SO₂-A wherein A is selected from the group

consisting of

loweralkyl,

aryl, and

heterocycle

wherein the loweralkyl, aryl, and heterocycle are

unsubstituted or substituted with 1, 2, 3,

4, or 5 substituents independently

selected from the group consisting of

alkoxy,

halogen,

haloalkyl,

loweralkyl, and

nitro,

sulfhydryl,

thioxo, and

thioalkoxy,

L₅ is absent or selected from the group consisting of

(a) C₁-to-C₁₀-alkylene and

(b) C₂-to-C₁₆-alkenylene

wherein (a) and (b) are unsubstituted or substituted as

defined previously, and

R₅ is selected from the group consisting of

hydrogen,

alkanoyl wherein the alkanoyl is unsubstituted or

substituted with substituents selected from the

group consisting of aryl,

alkoxy,
alkoxyalkyl,
470 alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1, 2 or 3
substituents independently selected from the
group consisting of
aryl and
475 halogen,
alkylaminocarbonylalkyl wherein the
alkylaminocarbonylalkyl is unsubstituted or
substituted with 1 or 2 substituents
independently selected from the group consisting
480 of aryl,
(anthracenyl)alkyl,
aryl,
arylalkoxy,
arylalkyl wherein the arylalkyl is unsubstituted or
485 substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group
consisting of
alkoxy,
aryl,
490 carboxyl,
cyano,
halogen,
haloalkoxy,
haloalkyl,
495 nitro,
oxo, and
-L₁₁-C(R₁₄)(R_v)-C(O)OR₁₅,
(aryl)oyl wherein the (aryl)oyl is unsubstituted or
substituted with substituents selected from the
500 group consisting of halogen,
aryloxycarbonyl,
carboxaldehyde,
-C(O)NRR',
cycloalkoxycarbonyl,

505 cycloalkylaminocarbonyl,
 cycloalkylaminothiocarbonyl,
 cyanoalkyl,
 cyclolalkyl,
 cycloalkylalkyl wherein the cycloalkylalkyl is
 510 unsubstituted or substituted with 1 or 2 hydroxyl
 substituents,
 with the proviso that no two hydroxyls are attached to the
 same carbon,
 (cyclolalkyl)oyl,
 515 (9,10-dihydroanthracenyl)alkyl wherein the
 (9,10-dihydroanthracenyl)alkyl is unsubstituted
 or substituted with 1 or 2 oxo substituents,
 haloalkyl,
 heterocycle,
 520 (heterocyclic)alkyl wherein the (heterocyclic)alkyl is
 unsubstituted or substituted with 1, 2, 3, 4, or 5
 substituents selected from the group consisting of
 loweralkyl,
 (heterocyclic)oyl,
 525 loweralkyl, wherein the loweralkyl is unsubstituted
 or substituted with substituents selected from the
 group consisting of -NRR',
 -SO₂-A, and
 thioalkoxyalkyl;

530

(3) -L₄-S(O)_m-L₅- wherein L₄ and L₅ are defined previously and m is 0, 1,
 or 2,

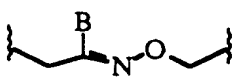
535 (4) -L₄-L₆-C(W)-N(R₆)-L₅- wherein L₄, W, and L₅ are defined previously,
 R₆ is selected from the group consisting of
 (a) hydrogen,
 (b) loweralkyl,
 (c) aryl,
 540 (d) arylalkyl,
 (e) heterocycle,

- (f) (heterocyclic)alkyl,
 (g) cyclolakyl, and
 (h) cycloalkylalkyl, and
 545 L_6 is absent or is selected from the group consisting of
 (a) -O-,
 (b) -S-, and
 (c) -N(R₆)- wherein R₆ is selected from the group
 consisting of
 550 hydrogen,
 loweralkyl,
 aryl,
 arylalkyl,
 heterocycle,
 555 (heterocyclic)alkyl,
 cyclolakyl, and
 cycloalkylalkyl,
- (5) -L₄-L₆-S(O)_m-N(R₅)-L₅-,
 560 (6) -L₄-L₆-N(R₅)-S(O)_m-L₅-,
 (7) -L₄-N(R₅)-C(W)-L₇-L₅- wherein L₄, R₅, W, and L₅ are
 defined previously and L₇ is absent or is selected from the group
 565 consisting of -O- and -S-,
 (8) C₁-C₁₀-alkylene wherein the alkylene group is unsubstituted or
 substituted with 1 or 2 substituents independently selected from
 the group consisting of
 570 (a) aryl,
 (b) arylalkyl,
 (c) heterocycle,
 (d) (heterocyclic)alkyl,
 (e) cyclolakyl,
 575 (f) cycloalkylalkyl,
 (g) alkylthioalkyl, and
 (h) hydroxy,

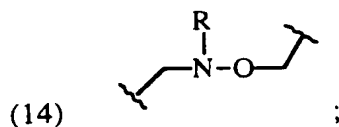
- (9) C₂-to-C₁₀-alkenylene wherein the alkenylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
- (a) aryl,
 - (b) arylalkyl,
 - (c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,
 - (d) heterocycle,
 - (e) (heterocycle)alkyl,
 - (f) hydroxyalkyl,
 - (g) cyclolalkyl,
 - (h) cycloalkylalkyl,
 - (i) alkylthioalkyl, and
 - (j) hydroxy,
- (10) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
- (a) aryl,
 - (b) arylalkyl,
 - (c) heterocycle,
 - (d) (heterocyclic)alkyl,
 - (e) cyclolalkyl,
 - (f) cycloalkylalkyl,
 - (g) alkylthioalkyl, and
 - (h) hydroxy,

(11) -L₄-heterocycle-L₅-,

(12) a covalent bond,

(13)  wherein B is selected from the group consisting of loweralkyl and arylalkyl, and

615



Z is selected from the group consisting of

- (1) a covalent bond,
- 620 (2) -O-,
- (3) -S(O)_q-, and
- (4) -NR_z- wherein R_z is selected from the group consisting of
 - (a) hydrogen
 - (b) loweralkyl,
 - 625 (c) aryl,
 - (d) arylalkyl,
 - (e) heterocycle,
 - (f) (heterocyclic)alkyl,
 - (g) cyclolalkyl, and
 - 630 (h) cycloalkylalkyl;

R₃ is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- 635 (3) fluorenyl,
- (4) heterocycle,

wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

- (a) alkanoyl,
- 640 (b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
 - halogen,
 - aryl, and
 - 645 cycloalkyl,
- (c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2, 3, 4 or 5 substituents independently selected from the group consisting of aryl and

- 650 cycloalkyl,
- (d) alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of aryl, and
- 655 cycloalkyl,
- (e) alkylsilyloxyalkyl,
- (f) arylalkyl,
- (g) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
- 660 alkanoyl,
- alkoxy wherein the alkoxy is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of cycloalkyl,
- 665 carboxaldehyde,
- haloalkyl,
- halogen,
- loweralkyl,
- nitro,
- 670 -NRR', and
- thioalkoxy,
- (h) arylalkyl,
- (i) aryloxy wherein the aryloxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of,
- 675 halogen,
- nitro, and
- NRR',
- (j) (aryl)oyl,
- 680 (k) carboxaldehyde,
- (l) carboxy,
- (m) carboxyalkyl,
- (n) -C(O)NRR" wherein R is defined previously and R" is selected from the group consisting of
- 685 hydrogen,
- loweralkyl, and

- carboxyalkyl,
- (o) cyano,
- (p) cyanoalkyl,
- 690 (q) cycloalkyl,
- (r) cycloalkylalkyl,
- (s) cycloalkoxyalkyl,
- (t) halogen,
- (u) haloalkyl wherein the haloalkyl is unsubstituted or substituted
- 695 with 1, 2, 3, 4, or 5 hydroxyl substituents,
- with the proviso that no two hydroxyls are attached to the same carbon,
- (v) heterocycle,
- (w) hydroxyl,
- 700 (x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or substituted with substituents selected from the group consisting of aryl,
- (y) loweralkyl wherein the loweralkyl is unsubstituted or substituted with substituents selected from the group consisting of
- 705 heterocycle,
- hydroxyl,
- with the proviso that no two hydroxyls are attached to the same carbon,
- NRR³RR^{3'}, and
- 710 -P(O)(OR)(OR'),
- (z) nitro,
- (aa) -NRR',
- (bb) oxo,
- (cc) -SO₂NR_A·R_B· wherein R_A· and R_B· are independently selected
- 715 from the group consisting of
- hydrogen,
- (aryl)oyl,
- loweralkyl, and
- heterocycle wherein the heterocycle is unsubstituted or
- 720 substituted with 1, 2, or 3 substituents
- independently selected from the group consisting of loweralkyl,
- (dd) sulfhydryl, and

(ee) thioalkoxy,

725

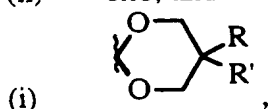
(5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from the group consisting of

730

- (a) alkoxy,
- (b) aryl,
- (c) arylalkoxy
- (d) aryloxy wherein the aryloxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,

735

- (e) loweralkyl,
- (f) halogen,
- (g) $\text{NR}^{\text{R3}}\text{R}^{\text{R3'}}$,
- (h) oxo, and



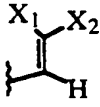
740

(6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

745

- (a) loweralkyl,
- (b) alkoxy,
- (c) halogen,
- (d) aryl,
- (e) aryloxy,
- (f) alkanoyl, and
- (g) $\text{NR}^{\text{R3}}\text{R}^{\text{R3'}}$,

750

(7)  wherein X_1 and X_2 together are cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of aryl, and

755

(8) $-\text{P}(\text{W})\text{R}^{\text{R3}}\text{R}^{\text{R3'}}$; and

R_4 is selected from the group consisting of

- (1) hydrogen,
(2) loweralkyl,
760 (3) haloalkyl
(4) halogen,
(5) aryl,
(6) arylalkyl,
(7) heterocycle,
765 (8) (heterocyclic)alkyl
(9) alkoxy, and
(10) -NRR'; or

L₁, Z, and R₃ together are selected from the group consisting of

- 770 (1) aminoalkyl,
(1) haloalkyl,
(2) halogen,
(3) carboxaldehyde, and
(4) (carboxaldehyde)alkyl, and
775 (5) hydroxyalkyl,

with the proviso that when **L₁, Z, and R₃** together are (1)-(5), **R₁** is other than hydrogen.

In a further aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with a pharmaceutically acceptable carrier.

780 In yet another aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.

In yet another aspect of the present invention is disclosed a method for inhibiting protein isoprenyl transferases (i.e., protein farnesyltransferase and/or
785 geranylgeranyltransferase) in a human or lower mammal, comprising administering to the patient a therapeutically effective amount of a compound compound of formula I.

In yet another aspect of the present invention is disclosed a method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase or both.

790 In yet another aspect of the present invention is disclosed a method for treatment of conditions mediated by farnesylated or geranylgeranylated proteins, for example, treatment of Ras associated tumors in humans and other mammals.

In yet another aspect of the present invention is disclosed a method for inhibiting or treating cancer in a human or lower mammal comprising administering to the patient a

795 therapeutically effective amount of a compound of the invention alone or in combination with another chemotherapeutic agent

In yet another aspect of the present invention is disclosed a method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

800 The compounds of the invention can comprise asymmetrically substituted carbon atoms. As a result, all stereoisomers of the compounds of the invention are meant to be included in the invention, including racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30, which is hereby incorporated herein by reference.

Detailed Description

810 Definitions of Terms

As used herein the terms "Cys," "Glu," "Leu," "Lys," "Met," "nor-Leu," "nor-Val," "Phe," "Ser" and "Val" refer to cysteine, glutamine, leucine, lysine, methionine, norleucine, norvaline, phenylalanine, serine and valine in their L-, D- or DL forms. As used herein these amino acids are in their naturally occurring L- form.

815 As used herein, the term "carboxy protecting group" refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy protecting group can be used as a prodrug whereby the carboxy protecting group can be readily cleaved *in vivo* (for example by enzymatic hydrolysis) to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by reference. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields (as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference). Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press, New York (1987), which is hereby incorporated herein by reference.

Representative carboxy protecting groups are C₁ to C₈ loweralkyl (e.g., methyl, ethyl or tertiary butyl and the like); arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxy)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl or cycloalkyloxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl or cycloalkyloxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like; aryloxycarbonyloxyalkyl, such as 2-(phenoxycarbonyloxy)ethyl, 2-(5-indanyloxycarbonyloxy)ethyl and the like; alkoxyalkylcarbonyloxyalkyl, such as 2-(1-methoxy-2-methylpropan-2-oyloxy)ethyl and the like; arylalkyloxycarbonyloxyalkyl, such as 2-(benzyloxycarbonyloxy)ethyl and the like; arylalkenyloxycarbonyloxyalkyl, such as 2-(3-phenylpropen-2-yloxycarbonyloxy)ethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

Preferred carboxy-protected compounds of the invention are compounds wherein the protected carboxy group is a loweralkyl, cycloalkyl or arylalkyl ester, for example, methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, sec-butyl ester, isobutyl ester, amyl ester, isoamyl ester, octyl ester, cyclohexyl ester, phenylethyl ester and the like or an alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl or an arylalkylcarbonyloxyalkyl ester.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated herein by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxycarbonyl, a-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, a,a-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "alkanoyl" as used herein refers to $R_{29}C(O)-$ wherein R_{29} is a loweralkyl group. The alkanoyl groups of this invention can be optionally substituted.

The term "alkanoylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{71}-NH-$ wherein R_{71} is an alkanoyl group. The alkanoylaminoalkyl groups of this invention can be optionally substituted.

The term "alkanoyloxy" as used herein refers to $R_{29}C(O)-O-$ wherein R_{29} is a loweralkyl group. The alkanoyloxy groups of this invention can be optionally substituted.

The term "alkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an alkanoyloxy group. The alkanoyloxyalkyl groups of this invention can be optionally substituted.

The term "alkenyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenyl include $-CH=CH_2$, $-CH_2CH=CH_2$, $-C(CH_3)=CH_2$,

905 -CH₂CH=CHCH₃, and the like. The alkenyl groups of this invention can be optionally substituted.

The term "alkenylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 20 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenylene include
910 -CH=CH-, -CH₂CH=CH-, -C(CH₃)=CH-, -CH₂CH=CHCH₂-, and the like. The alkenylene groups of this invention can be optionally substituted.

The term "alkenyloxy" as used herein refers to an alkenyl group attached to the parent molecular group through an oxygen atom. The alkenyloxy groups of this invention can be optionally substituted.

915 The term "alkenyloxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkenyloxy group. The alkenyloxyalkyl groups of this invention can be optionally substituted.

The term "alkoxy" as used herein refers to R₃₀O- wherein R₃₀ is loweralkyl as defined above. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy and the like. The alkoxy groups of this invention can be optionally substituted.
920

The term "alkoxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkoxy group. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkoxy" as used herein refers to R₃₁O-R₃₂O- wherein R₃₁ is loweralkyl as defined above and R₃₂ is an alkylene radical. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like. The alkoxyalkoxy groups of this invention can be optionally substituted.
925

The term "alkoxyalkyl" as used herein refers to an alkoxy group as previously defined appended to an alkyl group as previously defined. Examples of alkoxyalkyl
930 include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R₆₆-C(O)-O- wherein R₆₆ is an alkoxyalkyl group.

The term "alkoxyarylalkyl" as used herein refers to a an arylalkyl group to which is
935 attached an alkoxy group. The alkoxyarylalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonyl" as used herein refers to an alkoxy group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the
940 like. The alkoxycarbonyl groups of this invention can be optionally substituted. The alkoxycarbonyl groups of this invention can be optionally substituted.

The term "alkoxycarbonylalkyl" as used herein refers to an alkoxycarbonyl group as previously defined appended to a loweralkyl radical. Examples of alkoxycarbonylalkyl include methoxycarbonylmethyl, 2-ethoxycarbonylethyl and the like. The
 945 alkoxycarbonylalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{69}\text{-NH-}$ wherein R_{69} is an alkoxycarbonyl group. The
 alkoxycarbonylaminoalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to
 950 which is appended $R_{63}\text{-O-}$ wherein R_{63} is an alkoxycarbonyl group. The
 alkoxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "alkylamino" as used herein refers to $R_{35}\text{NH-}$ wherein R_{35} is a loweralkyl group, for example, methylamino, ethylamino, butylamino, and the like. The alkylamino
 groups of this invention can be optionally substituted.

The term "alkylaminoalkyl" as used herein refers a loweralkyl radical to which is
 955 appended an alkylamino group. The alkylaminoalkyl groups of this invention can be
 optionally substituted.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to a loweralkyl
 radical to which is appended $R_{70}\text{-C(O)-NH-}$ wherein R_{70} is an alkylamino group. The
 960 alkylaminocarbonylaminoalkyl groups of this invention can be optionally substituted.

The term "alkylene" as used herein refers to a divalent group derived from a straight
 or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal
 of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene,
 2,2-dimethylpropylene, and the like. The alkylene groups of this invention can be
 965 optionally substituted.

The term "alkylsilyloxy" as used herein refers to a loweralkyl group to which is
 attached $\text{-OSiR}_W\text{R}_X\text{R}_Y$ wherein R_W , R_X , and R_Y are selected from the group consisting
 of loweralkyl.

The term "alkylsulfinyl" as used herein refers to $R_{33}\text{S(O)-}$ wherein R_{33} is a
 970 loweralkyl group. The alkylsulfinyl groups of this invention can be optionally substituted.

The term "alkylsulfinylalkyl" as used herein refers to an alkyl group to which is
 attached a alkylsulfinyl group. The alkylsulfinylalkyl groups of this invention can be
 optionally substituted.

The term "alkylsulfonyl" as used herein refers to $R_{34}\text{S(O)}_2\text{-}$ wherein R_{34} is a
 975 loweralkyl group. The alkylsulfonyl groups of this invention can be optionally substituted.

The term "alkylsulfonylalkyl" as used herein refers to a loweralkyl radical to which
 is appended an alkylsulfonyl group. The alkylsulfonylalkyl groups of this invention can be
 optionally substituted.

980 The term alkylthioalkyl as used herein refers to a lower alkyl group as defined herein attached to the parent molecular moiety through a sulfur atom and an alkylene group. The alkylthioalkyl groups of this invention can be optionally substituted.

The term "alkynyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynyl include $-C\equiv CH$, $-CH_2C\equiv CH$, $-CH_2C\equiv CCH_3$, and the like.
985 The alkynyl groups of this invention can be optionally substituted.

The term "alkynylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynylene include $-C\equiv C-$, $-CH_2C\equiv C-$, $-CH_2C\equiv CCH_2-$, and the like. The alkynylene groups of this invention can be
990 optionally substituted.

The term "amino" as used herein refers to $-NH_2$.

The term "aminocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a carbonyl group. The aminocarbonyl groups of this invention can be optionally substituted.

995 The term "aminocarbonylalkyl" as used herein refers to an alkyl group to which is attached an aminocarbonyl group. The aminocarbonylalkyl groups of this invention can be optionally substituted.

The term "aminoalkyl" as used herein refers to a loweralkyl radical to which is appended an amino group. The aminoalkyl groups of this invention can be optionally
1000 substituted.

The term "aminothiocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a thiocarbonylcarbonyl ($C=S$) group. The aminothiocarbonyl groups of this invention can be optionally substituted.

The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an aryloxy group (i.e., $R_{61}-C(O)O-$ wherein R_{61} is an aryl group). The
1005 aryloxyalkyl groups of this invention can be optionally substituted.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups (including bicyclic aryl
1010 groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, sulfhydryl, nitro, cyano, carboxaldehyde, carboxy, alkoxycarbonyl, haloalkyl- $C(O)-NH-$, haloalkenyl- $C(O)-NH-$ and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

1015 The term "arylalkenyl" as used herein refers to an alkenyl radical to which is appended an aryl group. The arylalkenyl groups of this invention can be optionally substituted.

1020 The term "arylalkenyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{68}-O-C(O)-O-$ wherein R_{68} is an arylalkenyl group. The arylalkenyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "arylalkoxy" as used herein refers to an alkoxy group to which is attached an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

1025 The term "arylalkyl" as used herein refers to a loweralkyl radical to which is appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl and the like. The arylalkyl groups of this invention can be optionally substituted.

1030 The term "arylalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkylcarbonyloxy group (i.e., $R_{62}C(O)O-$ wherein R_{62} is an arylalkyl group). The arylalkylcarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxy" as used herein refers to an aryl group attached to the parent molecular group through an oxygen atom. The aryloxy groups of this invention can be optionally substituted.

1035 The term "aryloxycarbonyl" as used herein refers to an aryloxy group attached to the parent molecular group through a carbonyl group. The aryloxycarbonyl groups of this invention can be optionally substituted.

The term "aryloyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The aryloyl groups of this invention can be optionally substituted.

1040 The term "arylalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{67}-O-C(O)-O-$ wherein R_{67} is an arylalkyl group. The arylalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1045 The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{65}-O-$ wherein R_{65} is an aryl group. The aryloxyalkyl groups of this invention can be optionally substituted.

The term "arylalkoxy" as used herein refers to an alkoxy radical to which is appended $R_{65}-O-$ wherein R_{65} is an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

1050 The term "arylalkyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkoxy group. The arylalkyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxy" as used herein refers to $R_{65}-O-$ wherein R_{65} is an aryl group. The aryloxy groups of this invention can be optionally substituted. The aryloxy groups of this invention can be optionally substituted.

1055 The term "(aryl)oyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The (aryl)oyl groups of this invention can be optionally substituted.

The term "aryloxythioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{75}-S-$ wherein R_{75} is an aryloxyalkyl group. The
1060 aryloxythioalkoxyalkyl groups of this invention can be optionally substituted.

The term "aryloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{65}-O-C(O)-O-$ wherein R_{65} is an aryl group. The aryloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1065 The term "arylsulfonyl" as used herein refers to $R_{36}S(O)_2-$ wherein R_{36} is an aryl group. The arylsulfonyl groups of this invention can be optionally substituted.

The term "arylsulfonyloxy" as used herein refers to $R_{37}S(O)_2O-$ wherein R_{37} is an aryl group. The arylsulfonyloxy groups of this invention can be optionally substituted.

The term "carboxy" as used herein refers to $-COOH$.

1070 The term "carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxy ($-COOH$) group. The carboxyalkyl groups of this invention can be optionally substituted.

The term "cyanoalkyl" as used herein used herein refers to a loweralkyl radical to which is appended a cyano ($-CN$) group. The cyanoalkyl groups of this invention can be optionally substituted.

1075 The term "carboxaldehyde" as used herein used herein refers to $-CHO$.

The term "(carboxaldehyde)alkyl" as used herein used herein refers to a carboxaldehyde group attached to a loweralkyl group. The (carboxaldehyde)alkyl groups of this invention can be optionally substituted.

1080 The terms "cycloalkanoyl" and "(cycloalkyl)oyl" refer to a cycloalkyl group attached to the parent molecular group through a carbonyl group. The cycloalkanoyl and (cycloalkyl)oyl groups of this invention can be optionally substituted.

The term "cycloalkanoylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkanoyl group (i.e., $R_{60}-C(O)-$ wherein R_{60} is a cycloalkyl group). The cycloalkanoylalkyl groups of this invention can be optionally substituted.

1085 The term "cycloalkylalkoxyalkyl" as used herein refers to an alkoxyalkyl group to which is attached a cycloalkyl group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1090 The term "cycloalkenyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms and containing a carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like. The cycloalkenyl groups of this invention can be optionally substituted.

The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through an oxygen atom. The cycloalkoxy groups of this invention can be optionally substituted.

1095 The term "cycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a cycloalkoxy group. The cycloalkoxyalkyl groups of this invention can be optionally substituted.

1100 The term "cycloalkoxycarbonyl" as used herein refers to a cycloalkoxy group attached to the parent molecular group through a carbonyl group. The cycloalkoxycarbonyl groups of this invention can be optionally substituted.

1105 The term "cycloalkyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl and the like. The cycloalkyl groups of this invention can be optionally substituted. The cycloalkyl groups of this invention can be optionally substituted.

The term "cycloalkylaminocarbonyl" as used herein refers to $\text{NHR}_{60}\text{C(O)-}$ wherein R_{60} is a cycloalkyl group. The cycloalkylaminocarbonyl groups of this invention can be optionally substituted.

1110 The term "cycloalkylaminothiocarbonyl" as used herein refers to $\text{NHR}_{60}\text{C(S)-}$ wherein R_{60} is defined above. The cycloalkylaminothiocarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylalkoxy" as used herein refers to an alkoxy radical to which is appended a cycloalkyl group. The cycloalkylalkoxy groups of this invention can be optionally substituted.

1115 The term "cycloalkylalkoxyalkyl" as used herein refers to an alkyl radical to which is appended a cycloalkylalkoxy group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1120 The term "cycloalkylalkoxycarbonyl" as used herein refers to a cycloalkylalkoxy radical attached to the parent molecular group through a carbonyl group. The cycloalkylalkoxycarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkyl group. Representative examples of cycloalkylalkyl include cyclopropylmethyl, cyclohexylmethyl, 2-(cyclopropyl)ethyl, adamantylmethyl and the like. The cycloalkylalkyl groups of this invention can be optionally substituted.

1125 The term "cycloalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{64}-O-C(\ddot{O})-O-$ wherein R_{64} is a cycloalkyl group. The cycloalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "dialkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two alkoxy groups. The dialkoxyalkyl groups of this invention can be optionally substituted.

1130 The term "dialkylamino" as used herein refers to $R_{38}R_{39}N-$ wherein R_{38} and R_{39} are independently selected from loweralkyl, for example dimethylamino, diethylamino, methyl propylamino, and the like. The dialkylamino groups of this invention can be optionally substituted.

1135 The term "dialkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended a dialkylamino group. The dialkylaminoalkyl groups of this invention can be optionally substituted.

The term "dialkyaminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{73}-C(O)-$ wherein R_{73} is a dialkylamino group. The dialkyaminocarbonylalkyl groups of this invention can be optionally substituted.

1140 The term "dioxoalkyl" as used herein refers to a loweralkyl radical which is substituted with two oxo ($=O$) groups. The dioxoalkyl groups of this invention can be optionally substituted.

The term "dithioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two thioalkoxy groups. The dithioalkoxyalkyl groups of this invention can be optionally substituted.

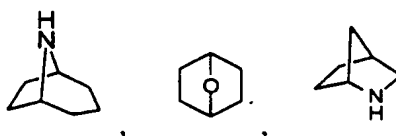
The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

1150 The term "haloalkenyl" as used herein refers to an alkenyl radical, as defined above, bearing at least one halogen substituent. The haloalkenyl groups of this invention can be optionally substituted.

The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like. Haloalkyl can also include perfluoroalkyl wherein all hydrogens of a loweralkyl group are replaced with fluorides.

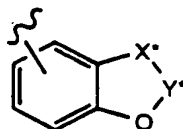
1155 The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to a 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur or a 5-membered ring containing 4 nitrogen atoms; and includes a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; two sulfur atoms in non-adjacent

positions; two sulfur atoms in adjacent positions and one nitrogen atom; two adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one oxygen atom. The 5-membered ring has 0-2 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The term "heterocyclic" also includes bicyclic, tricyclic and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from the group consisting of an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring and another monocyclic heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl or benzothienyl and the like). Heterocyclics include: pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyrimidyl, tetrahydrofuryl, dihydrofuryl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyranyl, dihydropyranyl, dithiazolyl, benzofuryl and benzothienyl. Heterocyclics also include bridged bicyclic groups wherein a monocyclic heterocyclic group is bridged by an alkylene group, for example,



and the like.

Heterocyclics also include compounds of the formula



wherein X* is -CH₂-, -CH₂O- or -O- and Y* is -C(O)- or -(C(R''))_v - wherein R'' is hydrogen or C₁-C₄-alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like.

Heterocyclics can be unsubstituted or substituted with one, two, three, four or five substituents independently selected from the group consisting of a) hydroxy, b) -SH, c) halo, d) oxo (=O), e) thioxo (=S), f) amino, g) -NHOH, h) alkylamino, i) dialkylamino, j) alkoxy, k) alkoxyalkoxy, l) haloalkyl, m) hydroxyalkyl, n) alkoxyalkyl, o) cycloalkyl which is unsubstituted or substituted with one, two, three or four

loweralkyl groups, p) cycloalkenyl which is unsubstituted or substituted with one, two, three or four loweralkyl groups, q) alkenyl, r) alkynyl, s) aryl, t) arylalkyl, u) -COOH, v) -SO₃H, w) loweralkyl, x) alkoxycarbonyl, y) -C(O)NH₂, z) -C(S)NH₂, aa) -C(=N-OH)NH₂, bb) aryl-L₁₆-C(O)- wherein L₁₆ is an alkenylene radical, cc) -S-L₁₇-C(O)OR₄₀ wherein L₁₇ is an alkylene radical which is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₂ is loweralkyl) and R₄₀ is hydrogen or a carboxy-protecting group, dd) -S-L₁₈-C(O)NR₄₃R₄₄ wherein L₁₈ is an alkylene radical which is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₃ and R₄₄ are independently selected from the group consisting of hydrogen, loweralkyl and aryl, ee) -S-L₁₉-CN wherein L₁₉ is an alkylene radical, ff) -S-L₂₀-R₄₅ wherein L₂₀ is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with oxo (=O) and R₄₅ is hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, gg) -O-L₂₁-R₄₆ wherein L₂₁ is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₆ is hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, hh) -O-S(O)₂-R₄₇ wherein R₄₇ is aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, ii) -S(O)₂-NH-R₄₈ wherein R₄₈ is aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, jj) alkylsulfinyl, kk) alkylsulfonyl, ll) arylsulfonyl, mm) arylsulfonyloxy, nn) -C(=NOR₄₉)C(O)OR₅₀ wherein R₄₉ is hydrogen or loweralkyl and R₅₀ is hydrogen or a carboxy-protecting group, oo) alkoxycarbonylalkyl,

pp) carboxyalkyl, qq) cyanoalkyl, rr) alkylaminoalkyl, ss) N-protected alkylaminoalkyl, tt) dialkylaminoalkyl, uu) dioxoalkyl, vv) loweralkyl-C(O)-, ww) loweralkyl-C(S)-, xx) aryl-C(O)-, yy) aryl-C(S)-, zz) loweralkyl-C(O)-O-, aaa) loweralkyl-S-C(S)- bbb) N-protected amino, ccc) aminoalkyl-C(O)-, ddd) N-protected aminoalkyl-C(O)- eee) aminoalkyl-C(S)-, 1235 fff) N-protected aminoalkyl-C(S)-, ggg) aminoalkyl, hhh) N-protected aminoalkyl, iii) formyl, jjj) cyano, kkk) nitro, lll) spiroalkyl, mmm) oxoalkyloxy, nnn) R_{53} - L_{22} -, wherein L_{22} is alkenylene or alkynylene and R_{53} is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, 1240 N-protected amino, alkoxy, thioalkoxy and haloalkyl, ooo) aryl-NH-C(O)-, ppp) R_{54} -N=N- wherein R_{54} is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, qqq) =N- R_{55} wherein R_{55} is hydrogen, 1245 aryl, heterocyclic, -S(O)₂-aryl or -S(O)₂-heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, rrr) diarylalkyl-N=N-, sss) aryl-N(R_{56})- or arylalkyl-N(R_{56})- wherein R_{56} is hydrogen or an N-protecting group, ttt) aryl-sulfonylalkyl, uuu) heterocyclicsulfonylalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, vvv) =C(CN)(C(O)NH₂), www) =C(CN)(C(O)O-loweralkyl), xxx) heterocyclic or heterocyclicalkyl wherein the heterocyclic 1255 is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, yyy) hydroxythioalkoxy, zzz) aryloxyalkyl, aaaa) aryloxyalkylthioalkoxy, bbbb) dialkoxyalkyl, cccc) dithioalkoxyalkyl, dddd) arylalkyl-NH- L_{23} - wherein L_{23} is an alkylene group, eeee) heterocyclicalkyl-NH- L_{24} - wherein L_{24} is an alkylene group, ffff) aryl-S(O)₂-NH- L_{25} - wherein L_{25} is an alkylene group, gggg) heterocyclic-S(O)₂-NH- L_{26} - wherein L_{26} is an alkylene group, hhhh) aryl-C(O)-NH- L_{27} - wherein L_{27} is an alkylene group and iiiii) heterocyclic-C(O)-NH- L_{28} - wherein L_{28} is an alkylene group, jjjj) $R_{yy}(\text{CH}_2)_n\text{-X-Y-Z-(CH}_2)_m$ wherein R_{yy} is cycloalkyl, aryl and loweralkyl, n and m are independently 0-2, Z is O or absent, Y is 1260 absent, CH₂, CHOH or C(O), with the proviso that when X is O, Z is absent and with the proviso that when Z is O, X is absent and with the proviso that when Y is CHOH, X and Z are absent.

The term "(heterocyclic)alkoxy" as used herein refers to an alkoxy group to which is attached a heterocycle. The (heterocyclic)alkoxy groups of this invention can be optionally substituted.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as defined above appended to a loweralkyl radical as defined above. Examples of heterocyclic alkyl include 2-pyridylmethyl, 4-pyridylmethyl, 4-quinolinylmethyl and the like. The (heterocyclic)alkyl groups of this invention can be optionally substituted.

The term "(heterocyclic)oxy" as used herein refers to a heterocycle connected to the parent molecular group through an oxygen atom. The (heterocyclic)oxy groups of this invention can be optionally substituted.

The term "(heterocyclic)oxyalkyl" as used herein refers to a loweralkyl group to which is attached a (heterocyclic)oxy group. The (heterocyclic)oxyalkyl groups of this invention can be optionally substituted.

The term "(heterocyclic)alkoxyalkyl" as used herein refers to an alkoxyalkyl group to which is attached a heterocycle. The (heterocyclic)alkoxyalkyl groups of this invention can be optionally substituted.

The term "heterocycliccarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{72}-C(O)-O-$ wherein R_{72} is a heterocyclic group. The heterocycliccarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "hydroxy" as used herein refers to $-OH$.

The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is appended an hydroxy group. The hydroxyalkyl groups of this invention can be optionally substituted.

The term "hydroxyarylalkyl" as used herein refers to a arylalkyl group to which is appended a hydroxy group. The hydroxyarylalkyl groups of this invention can be optionally substituted.

The term "hydroxythioalkoxy" as used herein refers to $R_{51}S-$ wherein R_{51} is a hydroxyalkyl group. The hydroxythioalkoxy groups of this invention can be optionally substituted.

The term "loweralkyl" as used herein refers to branched or straight chain alkyl groups comprising one to ten carbon atoms, including methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, neopentyl and the like. The loweralkyl groups of this invention can be optionally substituted.

The term "N-protected alkylaminoalkyl" as used herein refers to an alkylaminoalkyl group wherein the nitrogen is N-protected. The N-protected alkylaminoalkyl groups of this invention can be optionally substituted.

The term "nitro" as used herein refers to $-NO_2$.

1305 The term "oxo" as used herein refers to (=O).

The term "oxoalkyloxy" as used herein refers to an alkoxy radical wherein the loweralkyl moiety is substituted with an oxo (=O) group. The oxoalkyloxy groups of this invention can be optionally substituted.

1310 The term "oxyamino(alkyl)carbonylalkyl" as used herein refers to a -O-NR-C(O)-R' group wherein R and R' are loweralkyl.

The term "oxyamino(arylalkyl)carbonylalkyl" as used herein refers to a -O-NR^{R3}-C(O)-R group wherein R^{R3} is arylalkyl and R is loweralkyl.

The term "oxyaminocarbonylalkyl" as used herein refers to -O-NH-C(O)-R group wherein R is loweralkyl.

1315 The term "spiroalkyl" as used herein refers to an alkylene diradical, both ends of which are bonded to the same carbon atom of the parent group to form a spirocyclic group. The spiroalkyl groups of this invention can be optionally substituted.

The term "sulfhydryl" as used herein refers to -SH.

1320 The term "sulfhydrylalkyl" as used herein refers to a loweralkyl group to which is attached a sulfhydryl group. The sulfhydrylalkyl groups of this invention can be optionally substituted.

The term "thioalkoxy" as used herein refers to R₅₂S- wherein R₅₂ is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like. The thioalkoxy groups of this invention can be optionally substituted.

1325 The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group as previously defined appended to a loweralkyl group as previously defined. Examples of thioalkoxyalkyl include thiomethoxymethyl, 2-thiomethoxyethyl and the like. The thioalkoxyalkyl groups of this invention can be optionally substituted.

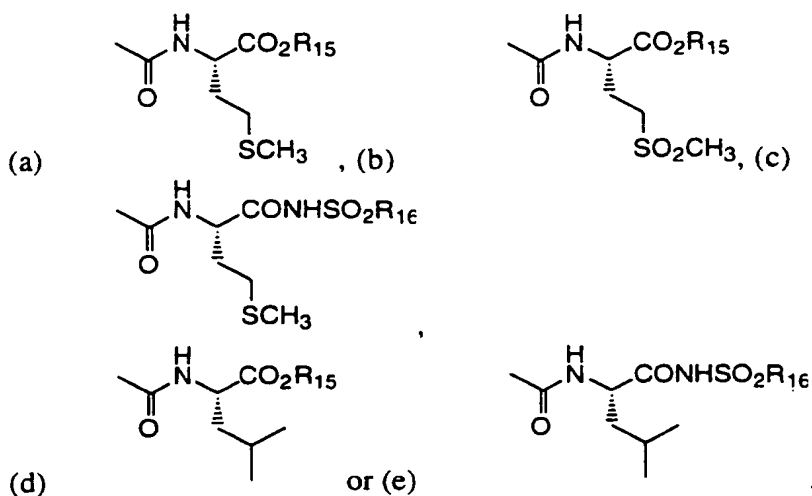
1330 The term "thiocycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through a sulfur atom. The thiocycloalkoxy groups of this invention can be optionally substituted.

The term "thiocycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a thiocycloalkoxy group. The thiocycloalkoxyalkyl groups of this invention can be optionally substituted.

1335 Preferred embodiments

Preferred compounds of the invention are compounds of formula I wherein R₁ is unsubstituted or substituted phenyl and R₂ is -C(O)NH-CH(R₁₄)-C(O)OR₁₅ or -C(O)NH-CH(R₁₄)-C(O)NHSO₂R₁₆ wherein R₂, R₁₄, R₁₅ and R₁₆ are defined above.

1340 More preferred compounds of the invention are compounds of formula I wherein R₁ is unsubstituted or substituted phenyl and R₂ is

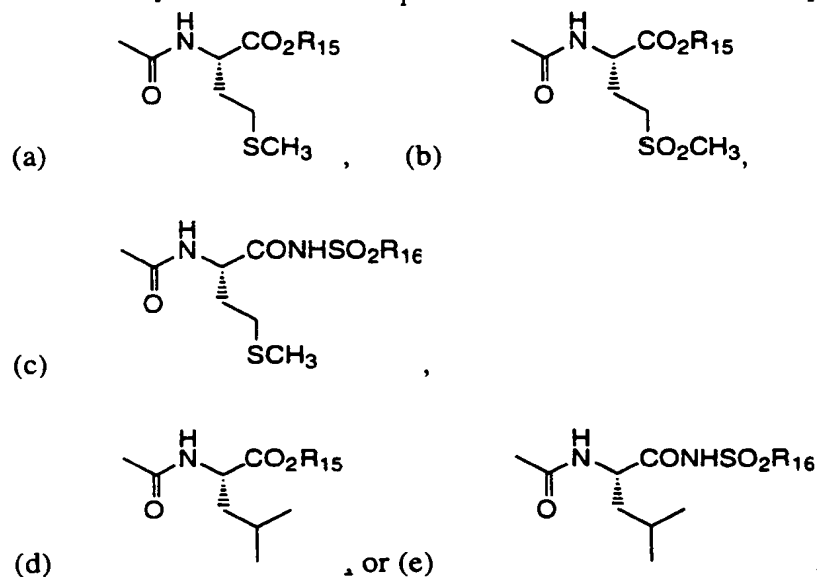


1345

Still more preferred compounds have formula I wherein R_3 is selected from the group consisting of (a) pyridyl, (b) imidazolyl, and (c) furyl wherein the pyridyl, imidazolyl, or furyl group may be substituted with 1, 2 or 3 substituents selected from the group consisting of aryl, loweralkyl, halo, nitro, haloalkyl, hydroxy, hydroxyalkyl, amino, N-protected amino, alkoxy, and thioalkoxy.

1350

Still more preferred compounds of the invention have the structure defined immediately above wherein R_1 is unsubstituted or substituted phenyl and R_2 is



1355

The most preferred compounds have the structure defined immediately above wherein R_3 is unsubstituted or substituted pyridyl or imidazolyl.

1360

Protein Farnesyltransferase Inhibition

The ability of the compounds of the invention to inhibit protein farnesyltransferase or protein geranylgeranyltransferase can be measured according to the method of Moores, et al., J. Biol. Chem. 266: 14603 (1991) or the method of Vogt, et al., J. Biol. Chem. 270:660-664 (1995). In addition, procedures for determination of the inhibition of farnesylation of the oncogene protein Ras are described by Goldstein, et al., J. Biol. Chem., 266:15575-15578 (1991) and by Singh in United States Patent No. 5,245,061.

In addition, *in vitro* inhibition of protein farnesyltransferase may be measured by the following procedure. Rat brain protein farnesyltransferase activity is measured using an Amersham Life Science commercial scintillation proximity assay kit and substituting a biotin-K Ras B fragment (biotin-Lys-Lys-Ser-Lys-Thr-Lys-Cys-Val-Ile-Met-CO₂H), 0.1 mM final concentration, for the biotin-lamin substrate provided by Amersham. The enzyme is purified according to Reiss, Y., et al., Cell, 62: 81-88 (1990), utilizing steps one through three. The specific activity of the enzyme is approximately 10 nmol substrate farnesylated/mg enzyme/hour. The percent inhibition of the farnesylation caused by the compounds of the invention (at 10×10^{-6} M) compared to an uninhibited control sample is evaluated in the same Amersham test system.

The % inhibition of protein farnesyltransferase was determined for representative compounds of the invention. The results are summarized in Table 1.

Tables 1-5

In Vitro Potencies of Representative Compounds

Table 1. Inhibition of farnesyltransferase

1385

Example	% inhibition at 1×10^{-5} M	Example	% inhibition at 1×10^{-5} M
200	93	674	40
350	53	676	76
351	82	678	73
352	52	680	58
353	62	683	57
354	47	684	48
355	43	685	55
356	58	686	48
357	56	687	78
358	45	688	71
359	36	689	73
360	88	690	61
361	97	692	74
362	83	699	74
363	96	700	68
364	69	701	64
365	97	702	79
366	83	704	67
367	81	705	72
368	71	706	53
369	87	707	66
370	86	708	76
371	66	709	55
372	69	710	45
373	76	711	46
374	61	712	69
375	68	713	40
376	80	714	56
377	71	715	67
378	54	717	75

380	45	718	40
381	79	750	44
382	> 50	752	58
383	> 50	753	55
387	> 50	754	40
388	> 50	755	44
390	> 50	756	47
639	44	757	58
659	55	758	46
663	43	759	49
664	75	952	> 50
669	52	955	50
670	78	974	> 50
672	48		

Table 2. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-6} M	Example	% inhibition at 1×10^{-6} M
157	92	583	98
158	2	587	97
159	84	595	97
160	30	607	96
161	54	610	94
162	12	613	97
163	18	617	99
164	92	620	98
165	74	626	61
166	97	627	85
167	98	632	43
168	92	633	32
183	98	636	72
184	36	641	34
185	93	642	48
186	86	644	54
187	68	386	> 50
188	40	399	> 50
189	88	403	99
190	4	404	98
191	28	405	98
192	95	406	95
193	4	407	98
196	43	435	96
197	1	451	85
201	63	452	96
202	31	453	90
203	76	456	81
204	98	457	92
205	98	460	88
206	67	463	91
207	98	465	92
208	98	466	93

209	74	467	97
210	5	468	96
211	98	469	92
212	12	470	95
213	98	471	94
214	97	472	97
215	82	473	96
216	67	474	92
217	99	475	21
218	89	476	91
219	56	477	98
220	92	478	98
221	55	479	95
222	41	480	87
223	63	481	95
224	41	488	41
225	93	494	96
226	23	495	95
227	94	496	93
228	39	497	94
231	50	498	98
233	65	499	98
234	4	500	98
235	95	501	84
237	98	502	24
238	22	503	57
239	97	504	90
240	98	505	72
241	41	507	95
242	99	507	96
243	23	508	95
244	21	509	77
245	50	510	84
248	79	512	94
249	77	513	96
250	96	514	94

252	98	515	72
253	99	516	95
254	96	525	99
255	98	528	99
256	98	529	99
257	98	530	94
258	98	537	97
259	98	540	40
260	98	645	37
261	98	646	58
262	98	649	86
263	99	650	68
264	98	651	33
265	98	652	41
266	97	653	62
267	96	655	35
268	98	657	32
269	98	658	73
270	98	661	45
271	84	662	68
272	96	665	55
273	96	666	82
274	94	667	83
276	98	671	36
277	98	673	59
278	99	677	37
279	99	682	31
280	98	691	34
281	98	693	53
282	76	694	45
283	98	696	57
284	83	697	39
286	84	703	40
287	24	716	69
288	22	719	90
289	23	720	70

290	74	721	83
291	23	722	96
292	36	723	87
294	98	724	87
295	94	725	78
296	89	726	81
297	65	727	95
298	43	744	84
299	94	749	84
300	22	751	32
301	98	764	88
302	31	765	76
304	99	768	67
305	99	771	72
306	99	772	79
307	82	773	41
308	62	774	48
309	98	775	32
310	98	776	36
311	97	777	83
313	94	782	96
314	97	786	34
315	93	787	70
316	63	788	44
317	54	789	86
318	98	790	88
319	98	791	53
320	93	792	88
321	90	793	94
322	98	794	92
323	98	796	35
324	98	797	35
325	99	806	72
326	91	807	90
327	97	808	88
328	96	809	78

329	98	810	89
330	98	812	94
331	98	813	95
332	26	816	87
333	99	824	90
334	93	831	92
343	72	832	80
344	95	834	55
345	91	835	96
346	98	844	92
347	95	846	85
348	66	850	90
349	99	862	95
379	21	866	62
541	37	867	71
542	67	868	89
544	35	872	74
545	88	878	95
546	97	879	95
547	91	886	35
550	96	889	95
	78	902	85
728			
552	88	903	78
553	92	908	88
554	96	910	42
555	85	911	65
556	99	918	97
557	93	923	78
560	91	924	77
561	91	925	87
564	98	926	69
565	94	936	
			69
566	98	937	95
568	93	962	> 50

569	91	964	> 50
572	91	979	26
575	70	982	64
576	88	987	93
577	94	988	92
582	99	989	88

1390 Table 3. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-7} M	Example	% inhibition at 1×10^{-7} M
434	93	623	96
436	89	729	73
437	89	730	96
438	90	731	65
439	80	732	84
440	92	733	60
441	91	734	49
442	88	735	96
443	97	736	96
444	95	737	95
445	94	738	54
446	91	739	83
447	91	740	94
448	92	741	89
449	91	742	87
450	96	743	51
455	83	745	93
458	87	746	84
459	92	747	68
461	93	748	56
462	91	769	90
464	86	770	91
482	96	781	91
483	95	785	96
484	97	795	87
485	96	798	95
486	97	799	96
487	81	800	74
489	86	801	87
490	70	802	88
491	94	811	85
492	95	814	81
493	51	815	71

511	82	817	60
519	89	818	78
520	97	822	93
521	94	823	75
522	93	825	79
523	97	839	63
524	99	849	66
526	96	854	78
527	97	855	92
531	74	856	97
532	88	857	92
533	91	859	86
534	84	861	65
535	89	863	72
536	79	864	84
539	89	865	95
548	86	869	92
549	98	874	90
551	93	875	92
558	87	876	92
559	96	891	94
562	95	893	87
563	95	894	89
570	92	895	92
571	88	896	96
573	72	900	95
574	81	906	88
578	90	912	85
579	92	913	89
580	90	914	91
581	96	917	78
584	96	919	91
585	96	921	82
589	91	929	81
590	95	931	98
592	93	933	91

593	86	935	72
594	95	940	92
597	75	941	90
600	93	945	80
601	92	947	79
602	97	948	75
604	86	949	57
609	95	950	71
611	95	951	71
615	94	959	> 50
616	95	983	66
618	89	984	86
621	98	990	84
622	95	993	90

Table 4. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-8} M	Example	% inhibition at 1×10^{-8} M
384	91	851	82
397	50	852	79
398	> 50	853	85
400	98	858	60
401	66	860	85
408	> 95	870	91
409	84	871	94
410	94	873	97
517	92	877	68
518	90	880	95
567	69	881	69
586	90	882	79
588	68	883	91
591	82	884	94
599	86	885	95
603	94	887	92
605	68	888	86
606	93	892	59
608	91	897	76
612	96	898	82
614	92	899	88
619	95	901	84
760	95	904	85
762	84	905	86
763	92	907	79
766	95	909	79
767	97	916	96
779	70	920	96
780	71	922	96
803	95	927	74
804	95	928	84
805	96	930	66
819	76	932	60

820	66	934	71
821	75	938	61
826	92	939	72
827	77	942	58
828	87	943	79
829	92	944	88
833	78	946	52
836	95	954	> 50
837	91	958	> 50
838	92	960	> 50
840	73	985	89
841	93	986	95
842	88	991	69
843	96	992	93
845	85	994	83
847	85	995	92
848	87	996	80

Table 5. Inhibition of geranylgeranyltransferase I.

Example	Activity
387	> 50% inhibition at 1×10^{-6} M
388	> 50% inhibition at 1×10^{-7} M
389	> 50% inhibition at 1×10^{-6} M
390	> 50% inhibition at 1×10^{-5} M
392	> 50% inhibition at 1×10^{-5} M
399	> 50% inhibition at 1×10^{-6} M
953	> 50% inhibition at 1×10^{-6} M
955	> 50% inhibition at 1×10^{-7} M
962	> 50% inhibition at 1×10^{-7} M
964	> 50% inhibition at 1×10^{-6} M
966	> 50% inhibition at 1×10^{-6} M
967	> 50% inhibition at 1×10^{-6} M
969	> 50% inhibition at 1×10^{-5} M
974	> 50% inhibition at 1×10^{-5} M

1395 Table 6. Inhibition of farnesyltransferase at concentrations of 10 mM and 1 mM unless specified as * (0.1 mM) or ** (0.01 mM)

Example	% inhibition 10 mM	% inhibition 1 mM	Example	% inhibition 10 mM	% inhibition 1 mM
997		91**	1199		71
998		79**	1200		97*
999		90	1201		73*
1000		82*	1202		96**
1001		92**	1203		84*
1002		82**	1204		93*
1003		92*	1205		55**
1004		92**	1206		63**
1005		95**	1207		91*
1006		95**	1208		89*
1007		85**	1209		87*
1008		95**	1210		64**
1009		86**	1211		94
1010		90*	1212		86*

1011		92**	1213		79**
1012		88*	1214		92**
1013		80*	1215		17
1014		91	1216		88**
1015		59*	1217		87*
1016		92*	1218		54**
1017		51*	1219		85**
1018		97	1220		
1019		70	1221		82**
1020		39	1222		89*
1021		93*	1223		91**
1022		91**	1224		88*
1023		89**	1225		92**
1024		89**	1226		69**
1025		91**	1227		91
1026		74**	1228		88*
1027		81**	1229		66**
1028		92**	1230		77**
1029		82**	1231		93*
1030		92**	1232		68**
1031		90**	1233		77**
1032		93**	1234		71**
1033		76**	1235		86**
1034		77	1236		83**
1035		76	1237		89**
1036		79	1238		91**
1037		88	1239		85*
1038		57	1240		64**
1039		89**	1241		74*
1040		90**	1242		75*
1041		48	1243		95*
1042		88	1244		84
1043		90*	1245		92
1044		76*	1246		82

1045		86*	1247		95*
1046		93	1248		88
1047		95	1249		89
1048		78**	1250		79**
1049		93**	1251		91**
1050		62**	1252		84*
1051		79**	1253		76*
1052		91**	1254		67
1053		60**	1255		82*
1054		89**	1256		95*
1055		85**	1257		93**
1056		75**	1258		97**
1057		82*	1259		89**
1058		89	1260		90**
1059		92*	1261		94
1060		42	1262		95
1061		88*	1263		85*
1062		93	1264		83**
1063		92**	1265		90
1064		95**	1266		85*
1065		78*	1267		96
1066		73**	1268		95*
1067		93*	1269		84**
1068		79**	1270		91**
1069		74*	1271		78**
1070		93**	1272		73**
1071		95*	1273		94*
1072		82*	1274		89*
1073		93**	1275		86**
1074		82	1276		88**
1075		90**	1277		90**
1076		69**	1278		68
1077		93**	1279		87**
1078		86*	1280		78**

1079		90	1281		81*
1080		87	1282		69*
1081		61	1283		74*
1082		84*	1284		86
1083		88	1285		94
1084		76**	1286		85**
1085		93*	1287		95**
1086		87*	1288		69*
1087		76*	1289		93
1088		73*	1290		80
1089		86*	1291		
1090		81**	1292		
1091		87*	1293		
1092		74**	1294		
1093		95**	1295		
1094		96**	1296		
1095		76*	1297		
1096		86*	1298		97**
1097		80**	1299		96**
1098		60*	1300		97*
1099		87**	1301		97*
1100		82**	1302		93**
1101		86*	1303		91**
1102		84**	1304		90**
1103		92*	1305		91**
1104		89**	1306		85**
1105		91**	1307		85**
1106		67**	1308		91**
1107		88**	1309		96*
1108		95**	1310		90**
1109		74**	1311		95**
1110			1312		91**
1111		63**	1313		91**
1112		62	1314		96*

1113		55	1315		86*
1114		83**	1316		78*
1115		94*	1317	99	96
1116		91**	1318		
1117		92*	1319		79**
1118		86*	1320		79
1119		84**	1321		
1120		93	1322		
1121		72*	1323		
1122		92**	1324		
1123		90*	1325		
1124		90*	1326		
1125		92*	1327		
1126		87	1328		
1127		90*	1329		
1128		86*	1330		
1129		92**	1331		
1130		88**	1332		92**
1131		96**	1333		95*
1132		97*	1334		72**
1133		75*	1335		90*
1134		95**	1336		74
1135		88*	1337		83**
1136		91	1338		65*
1137		83**	1339		
1138		65*	1340		77*
1139		92*	1341		89
1140		77**	1342		
1141		80*	1343		88
1142		84**	1344		93**
1143		92*	1345		94**
1144		76*	1346		94*
1145		83*	1347		81**
1146		61**	1348		78**

1147		93*	1349		92**
1148		79**	1350		
1149		94*	1351		
1150		92*	1352		
1151		91*	1353		
1152		96*	1354		38
1153		89*	1355		46
1154		93*	1356		80
1155		91*	1357		78
1156		87	1358		
1157		66**	1359		
1158	75		1360		98**
1159		72*	1361		96*
1160		83*	1362		83**
1161		87*	1363		88**
1162		84*	1364		
1163		73**	1365		
1164		94	1366		79*
1165		84*	1367		93*
1166		74**	1368		92**
1167		91*	1369		94*
1168		88*	1370		86**
1169		77	1371		94*
1170		74*	1372		95**
1171		74**	1373		95**
1172		38*	1374		93**
1173		89**	1375		80**
1174		79**	1376		86**
1175		96	1377		95*
1176		97*	1378		68
1177		19	1379		41
1178		88**	1380		87**
1179		85*	1381		65**
1180		93*	1382		86**

1181		82*	1383		88*
1182		92**	1384		69**
1183		79**	1385		93*
1184		84**	1386		88*
1185		85**	1387		82**
1186		93**	1392		93*
1187		93**	1397		87**
1188		93**	1398		81*
1189		74**	1399		94
1190		95**	1400		95
1191		85**			
1192		91*			
1193		95**			
1194		78**			
1195		94*			
1196		87*			
1197		85*			
1198		86*			

* % inhibition at 0.1 μ M

** % inhibition at 0.01 μ M

1400 Additional methods for the measurement of *in vitro* inhibition of protein prenylation (i.e., inhibition of farnesyltransferase or geranylgeranyltransferase) are described below.

Assays are performed using the glass fiber filter binding assay procedure with either rabbit reticulocyte lysate or FTase or GGTase I fractions isolated from bovine brains using a combination of hydrophobic and DEAE column chromatography procedures. Protein
 1405 substrates are purchased from Panvera Corporation (H-ras for FTase, H-ras-CVLL for GGTase I). Tritium labeled prenyl lipid substrates (FPP or GGPP) are obtained from Amersham Life Science.

FTase

1410 3 H-Farnesyldiphosphate (final concentration 0.6 μ M), H-Ras (final concentration 5.0 μ M) and the test compound (various final concentrations from a stock solution in 50% DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50 mM HEPES (pH 7.5), 30 mM $MgCl_2$, 20 mM KCl, 10 μ M $ZnCl_2$, 5 mM DTT, 0.01% Triton X-100) to give

1415 a final volume of 50 μ L. The mixture was brought to 37 °C, enzyme was added, and the reaction is incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the reaction, and the mixture was allowed to stand for 15 minutes at room temperature then diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass filter was transferred to a scintillation vial and 5 mL of scintillation fluid was added. The radioisotope retained on the glass fiber filter was counted to reflect the activity of the enzymes. The IC₅₀ value was calculated by measuring the activity of the enzyme over a suitable range of inhibitor concentrations.

GGTase I

1425 ³H-geranylgeranyldiphosphate (final concentration 0.5 μ M), H-Ras-CVLL (final concentration 5.0 μ M) and the test compound (various final concentrations from a stock solution in 1:1 DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50 mM Tris-HCl (pH 7.2), 30 mM MgCl₂, 20 mM KCl, 10 μ M ZnCl₂, 5 mM DTT, 0.01% Triton X-100) to give a final volume of 50 μ L. The mixture was brought to 37 °C, treated with enzyme, and incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the reaction, and the mixture was allowed to stand for 15 minutes at room temperature then diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass filter was transferred to a scintillation vial, and 5 mL scintillation fluid was added. The radioisotope retained on the glass fiber filter was counted to reflect the activity of the enzymes. The IC₅₀ value was calculated by measuring the activity of the enzyme over a suitable range of inhibitor concentrations.

1440 Additionally, the ability of the compounds of the invention to inhibit prenylation in whole cells, inhibit anchorage-independent tumor cell growth and inhibit human tumor xenograft in mice could be demonstrated according to the methods described in PCT Patent Application No. WO95/25086, published September 21, 1995, which is hereby incorporated herein by reference.

Pharmaceutical Compositions

1445 The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. These salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride,

1450

hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides (such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides), dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I)-(XII) or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Such pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful (in humans and other mammals) for inhibiting protein isoprenyltransferases (i.e, protein farnesyltransferase and/or protein geranylgeranyltransferase) and the isoprenylation (i.e., farnesylation and/or geranylgeranylation) of Ras. These inhibitors of protein isoprenyltransferases are also useful for inhibiting or treating cancer in humans and other mammals. Examples of cancers which may be treated with the compounds of the invention include, but are not limited to, carcinomas such as lung, colorectal, bladder, breast, kidney, ovarian, liver, exocrine pancreatic, cervical, esophageal, stomach and small intestinal; sarcomas such as oesteroma, osteosarcoma, lepoma, liposarcoma, hemanoma and hemangiosarcoma; melanomas such as amelanotic and melanotic; mixed types of cancers such as carcinosarcoma, lymphoid tissue type, follicular reticulum, cell sarcoma and Hodgkins disease and leukemias, such as

myeloid, acute lymphoblastic, chronic lymphocytic, acute myeloblastic and chronic myelocytic.

1490 The ability of the compounds of the invention to inhibit or treat cancer can be demonstrated according to the methods of Mazerska Z., Woynarowska B., Stefanska B., Borowski S., *Drugs Exptl. Clin. Res.* 13(6), 345-351 (1987) Bissery, M.C., Guenard F., Gueritte-Voegelein F., Lavelle F., *Cancer Res.* 51, 4845-4852 (1991) and Rygaard J., and Povlsen C., *Acta Pathol. Microbiol. Scand.* 77, 758 (1969), which are hereby incorporated herein by reference.

1495 These inhibitors of protein isoprenyltransferases are also useful for treating or preventing restenosis in humans and other mammals. The ability of the compounds of the invention to treat or prevent restenosis can be demonstrated according to the methods described by Kranzhofer, R. et al. *Circ. Res.* 73: 264-268 (1993), Mitsuka, M. et al. *Circ. Res.* 73: 269-275 (1993) and Santoian, E.C. et al. *Circulation* 88: 11-14 (1993),
1500 which are hereby incorporated herein by reference.

For use as a chemotherapeutic agent, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.01 to 500 mg/kg body weight daily, preferably in amounts from 0.1 to 20 mg/kg body weight daily and more preferably in amounts from 0.5 to 10 mg/kg body weight daily. Dosage unit compositions
1505 may contain such amounts of submultiples thereof to make up the daily dose.

For treatment or prevention of restenosis, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

1510 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally or topically in dosage unit formulations containing
1520 conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes

subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

1525 Injectable preparations, for example sterile injectable aqueous or oleagenous suspensions, may be formulated according to the known art using suitable dispersing or wetting and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent (as in a solution in 1,3-propanediol, for example). Among the acceptable vehicles and solvents
1530 that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Additionally, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid find use in the preparation of injectables.

1535 Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum and release the drug.

1540 Solid dosage forms for oral administration may include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. These dosage forms may also comprise additional substances other than inert diluents such as lubricating agents like magnesium stearate. With capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills may also be prepared with enteric coatings.

1545 Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions may also comprise adjuvants such as wetting agents, emulsifying and suspending agents and sweetening, flavoring, and perfuming agents.

1550 The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers,
1555 preservatives, excipients and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*, which is hereby incorporated herein by reference.

1560 While the compounds of the invention can be administered as the sole active pharmaceutical agent for the treatment of cancer, they can also be used in combination with one or more other chemotherapeutic agents.

Representative examples of chemotherapeutic agents are described in Holleb, et al., Clinical Oncology, American Cancer Society, United States (1991) p 56 *et seq.*, which is
1565 hereby incorporated herein by reference. These agents include alkylating agents such as the nitrogen mustards (mechloethamine, melphalan, chlorambucil, cyclophosphamide and ifosfamide), nitrosoureas (carmustine, lomustine, semustine, streptozocin), alkyl sulfonates (busulfan), triazines (dacarbazine) and ethylenimines (thiotepa, hexamethylmelamine); folic acid analogues (methotrexate); pyrimidine analogues (5-fluorouracil, cytosine arabinoside);
1570 purine analogues (6-mercaptopurine, 6-thioguanine); antitumor antibiotics (actinomycin D, the anthracyclines (doxorubicin), bleomycin, mitomycin C, methramycin); plant alkaloids such as vinca alkaloids (vincristine and vinblastine) and etoposide (VP-16); hormones and hormone antagonists (tamoxifen and corticosteroids); and miscellaneous agents (cisplatin, taxol and brequinar).

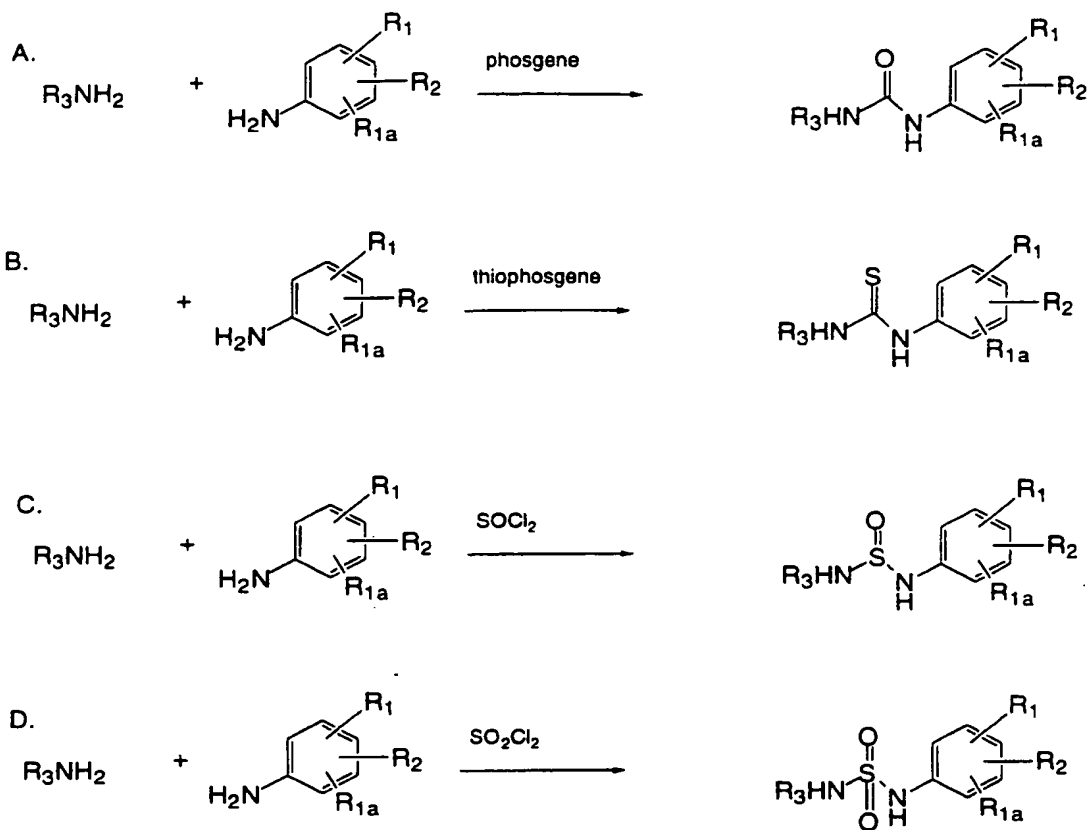
1575 The above compounds to be employed in combination with the isoprenyl protein transferase inhibitor of the invention will be used in therapeutic amounts as indicated in the Physicians' Desk Reference (PDR) 47th Edition (1993), which is incorporated herein by reference or by such therapeutically useful amounts as would be known to one of ordinary skill in the art.

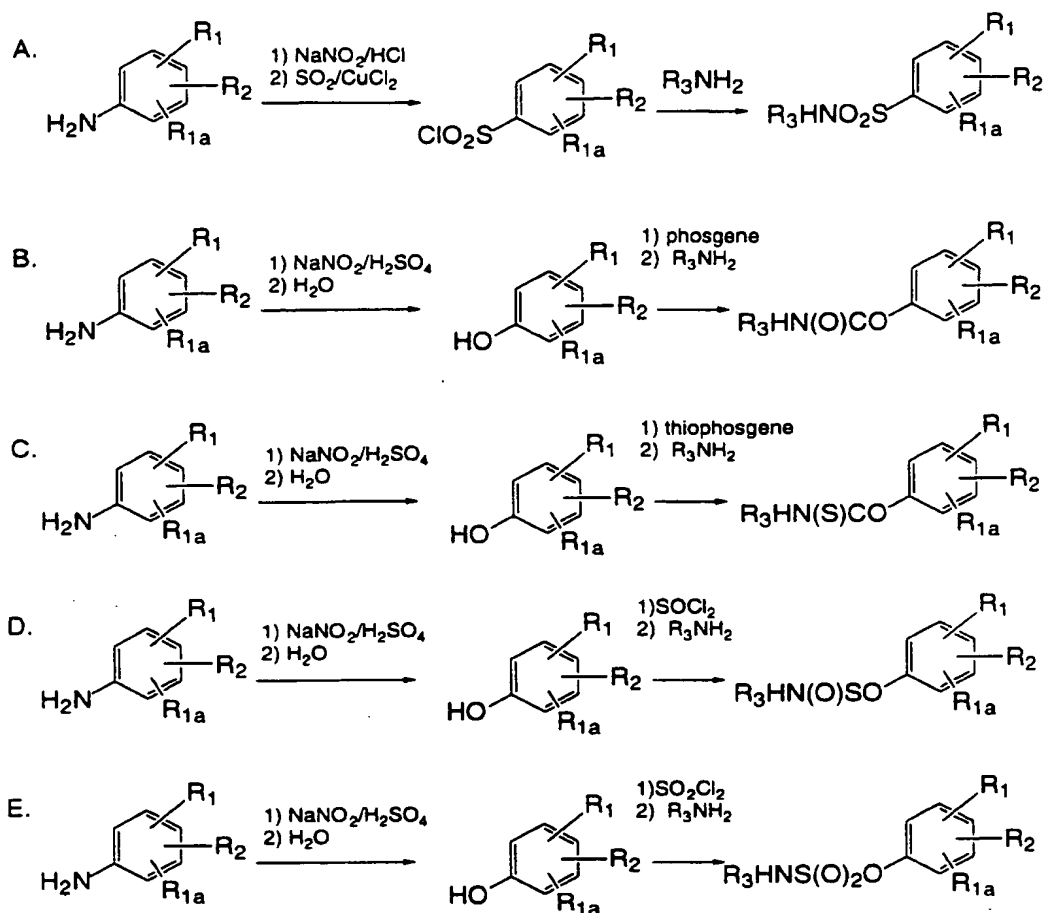
1580 The compounds of the invention and the other chemotherapeutic agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient.

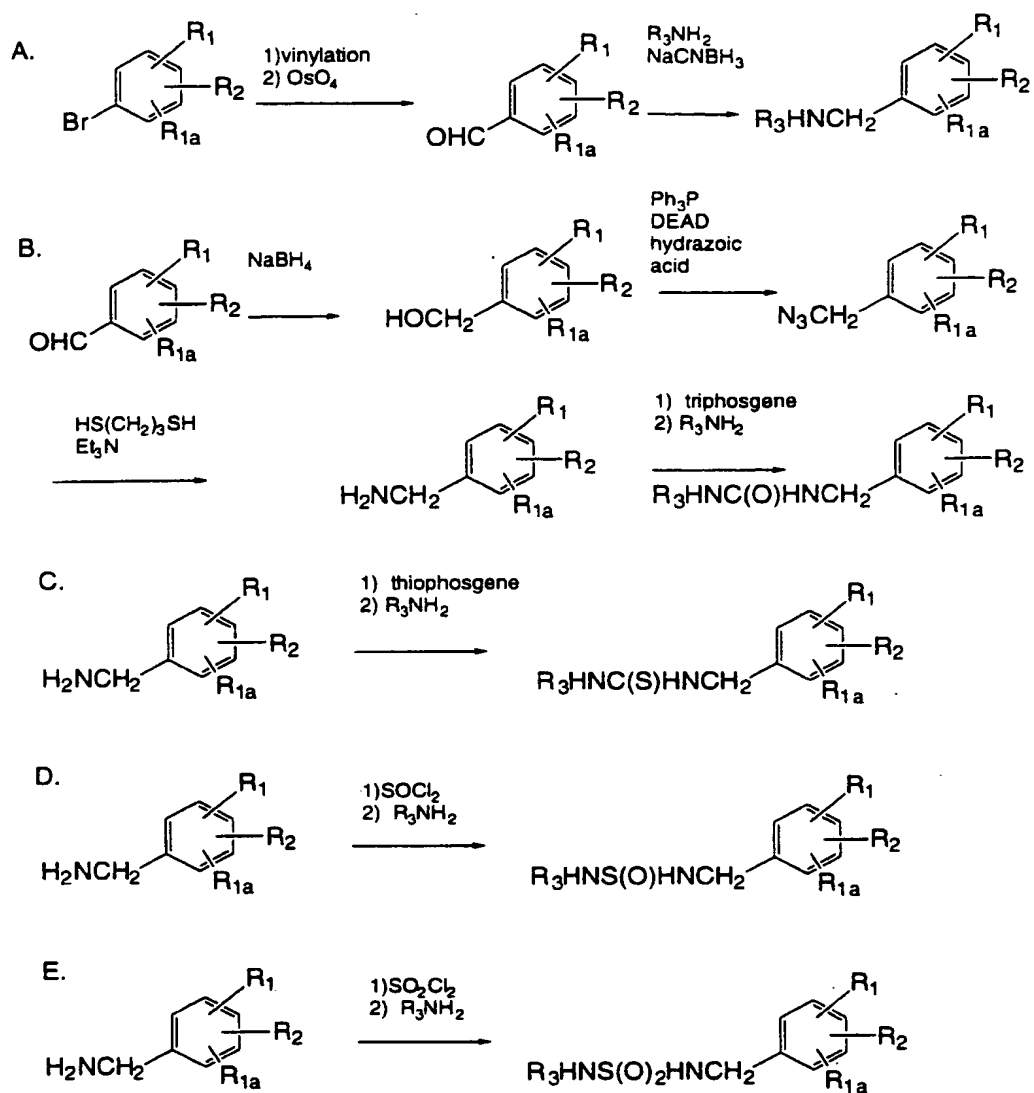
1585 When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

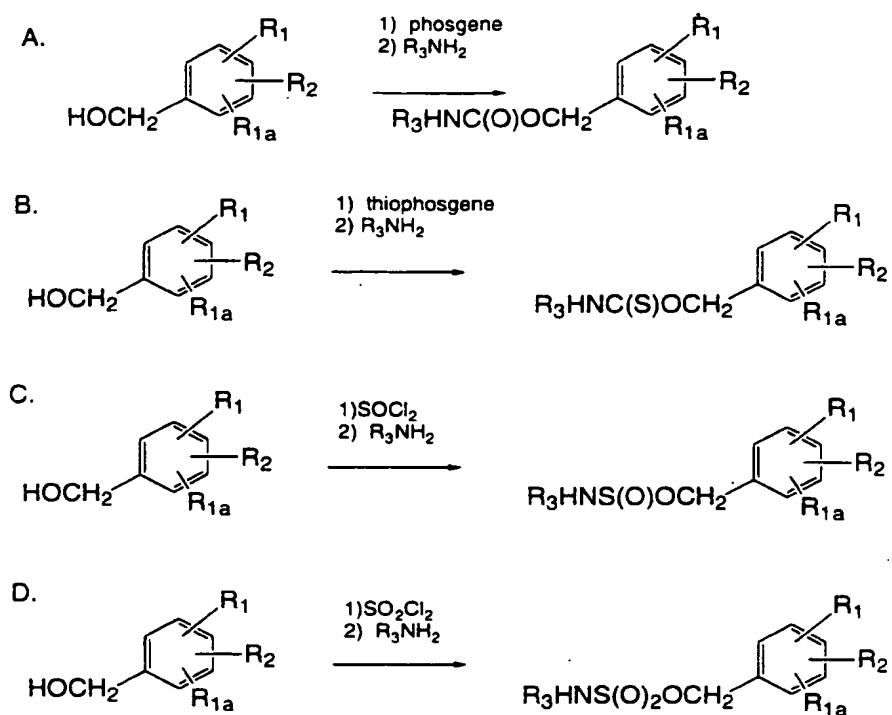
Preparation of the Compounds of the Invention

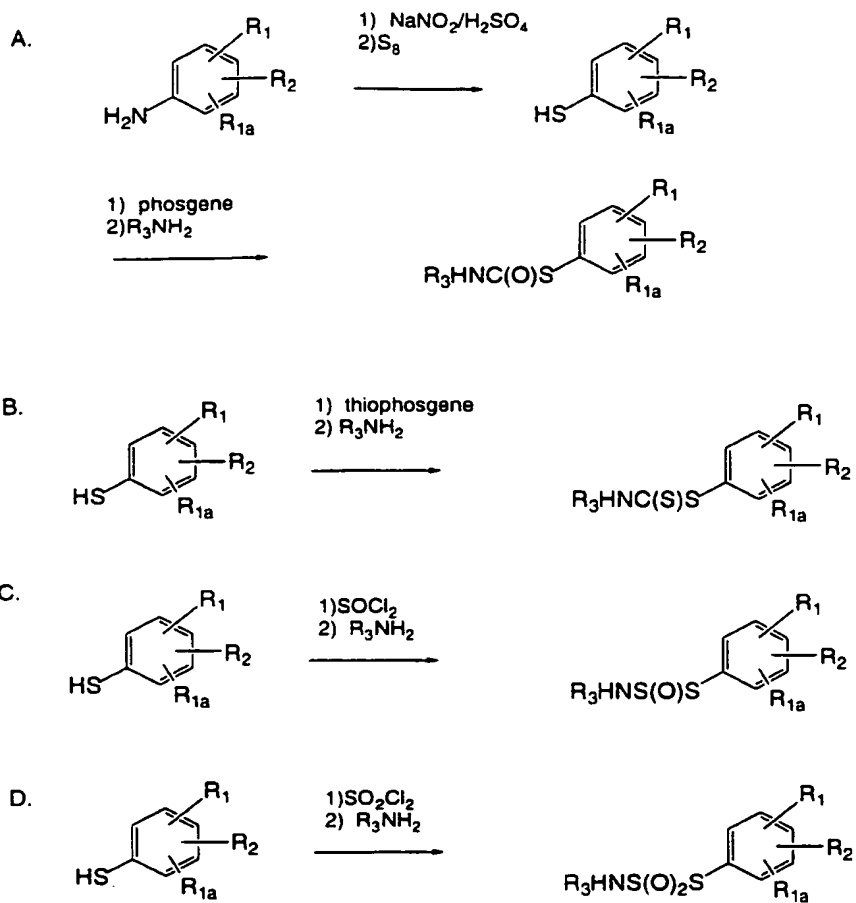
1590 In general, the compounds of the invention can be prepared by the processes illustrated in the following Schemes 1-16. In these general schemes compounds of the formula I are used to exemplify the methods, but the methods are intended to be applicable to all of the compounds of the invention.

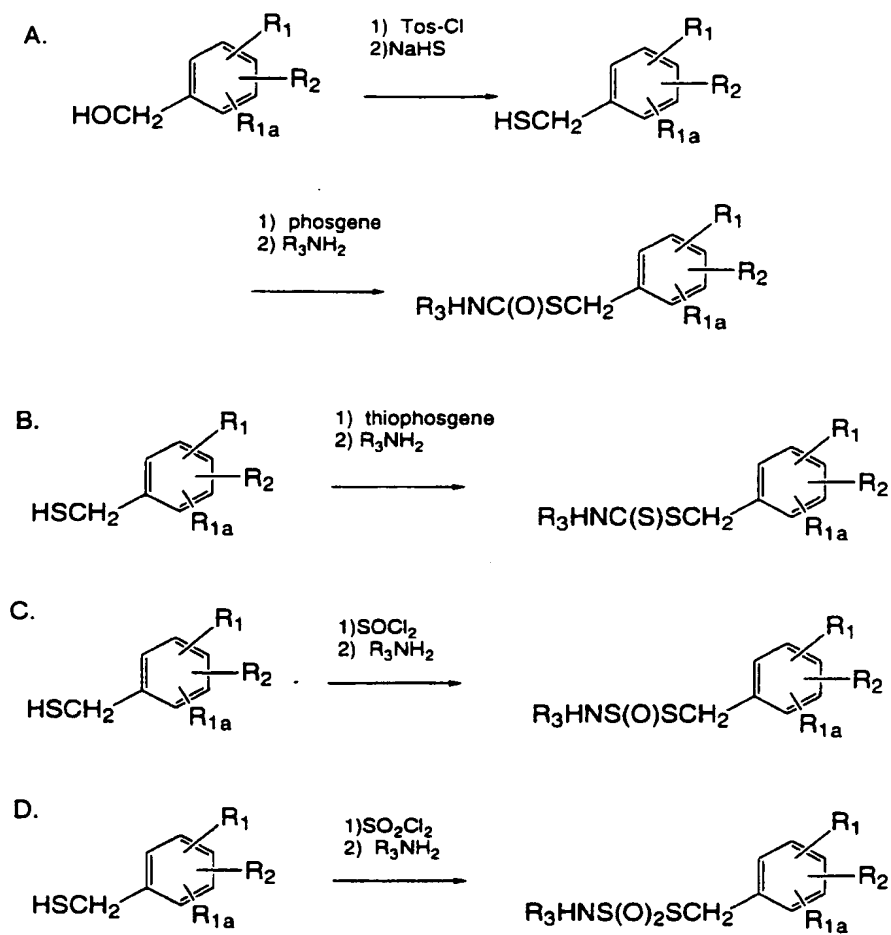
SCHEME 1

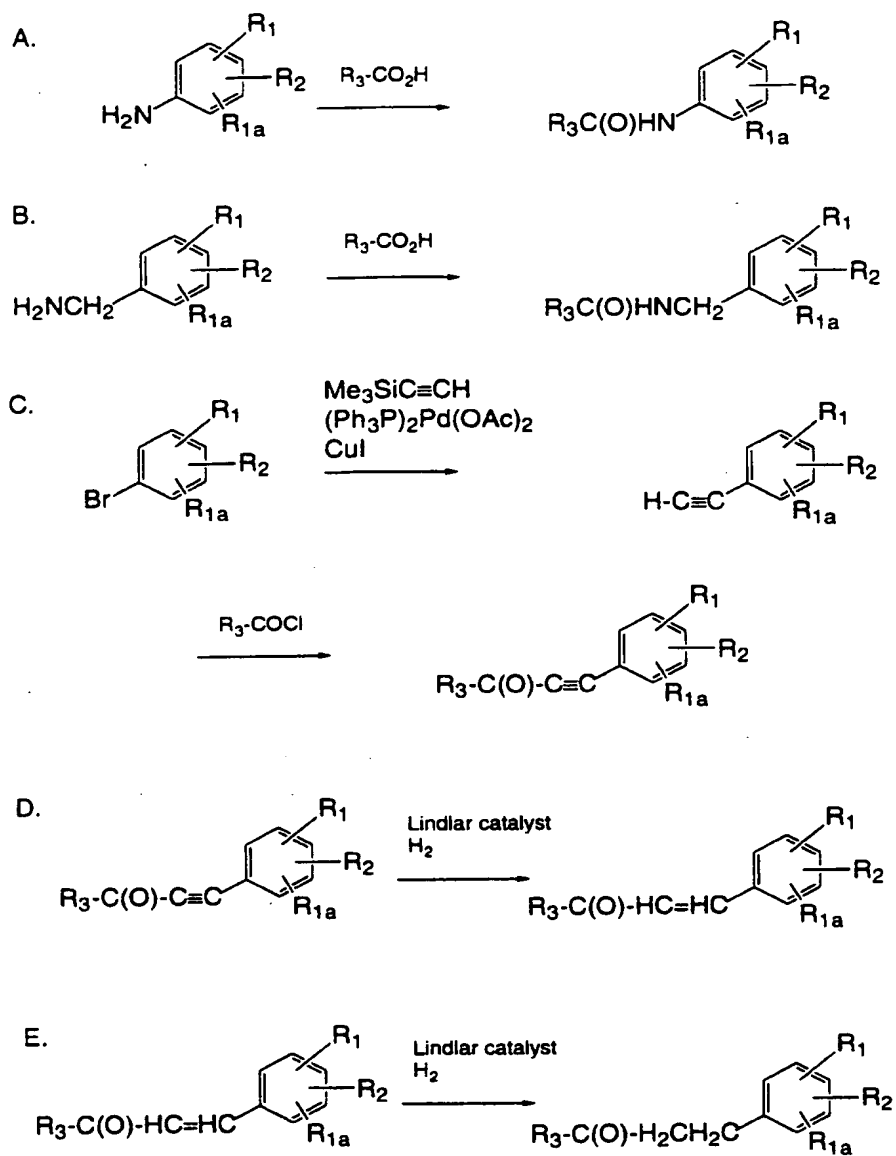
SCHEME 2

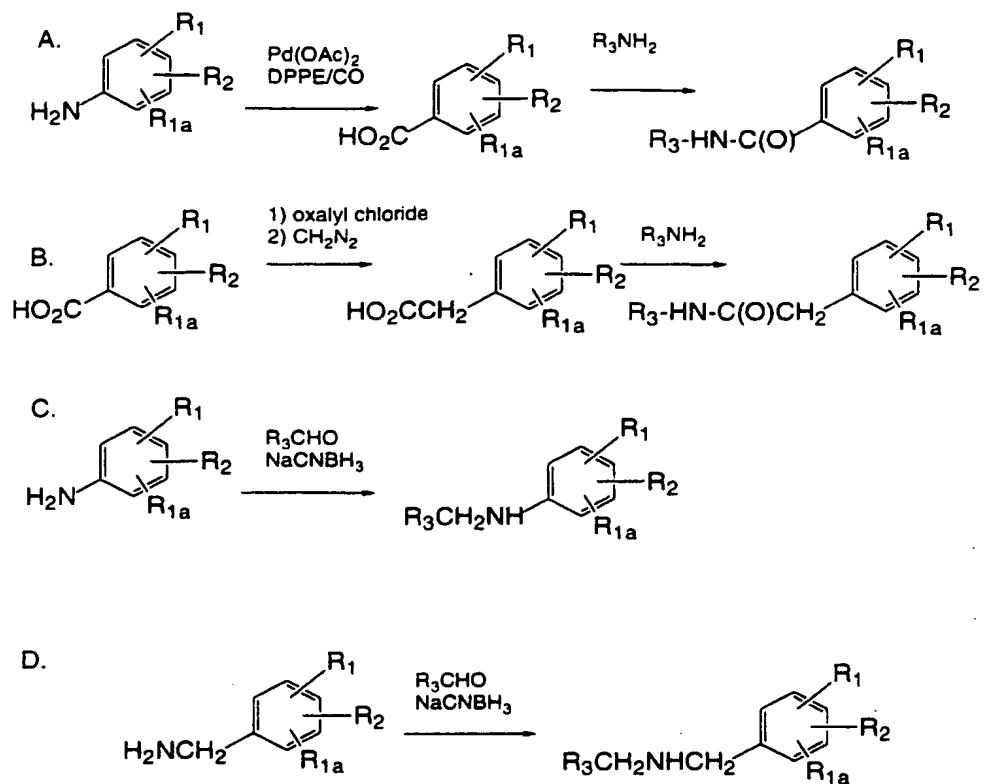
SCHEME 3

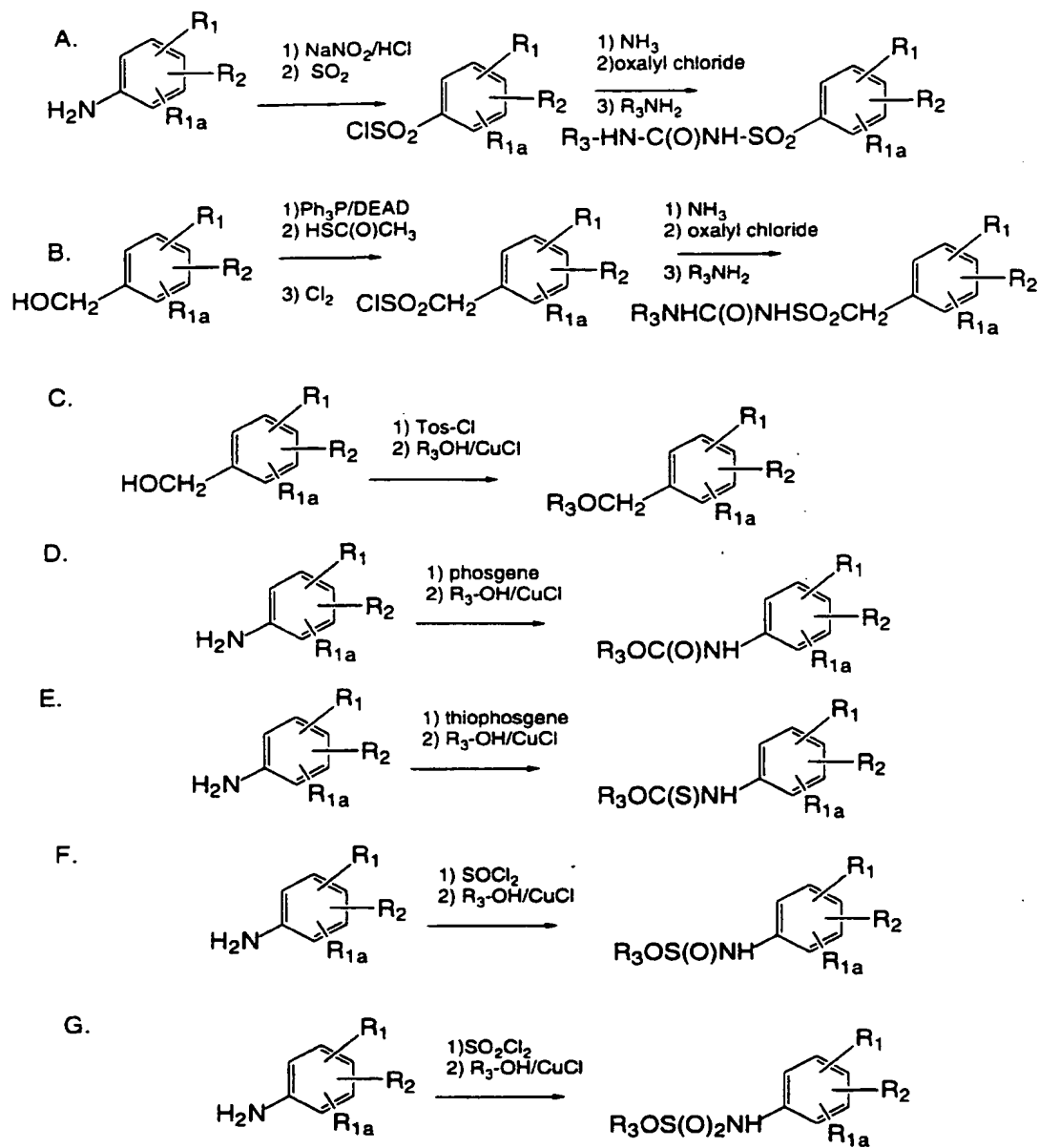
SCHEME 4

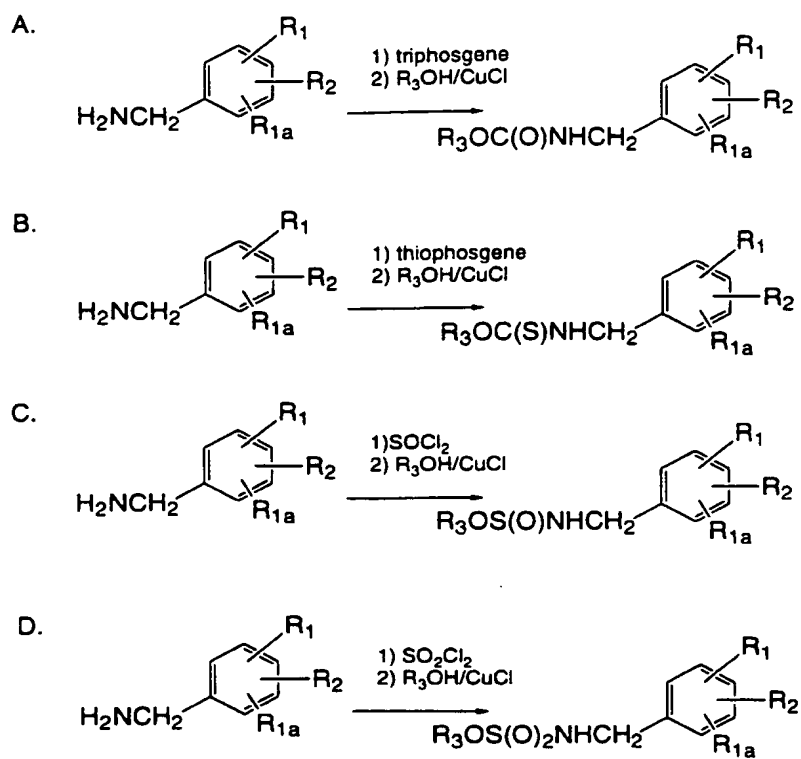
SCHEME 5

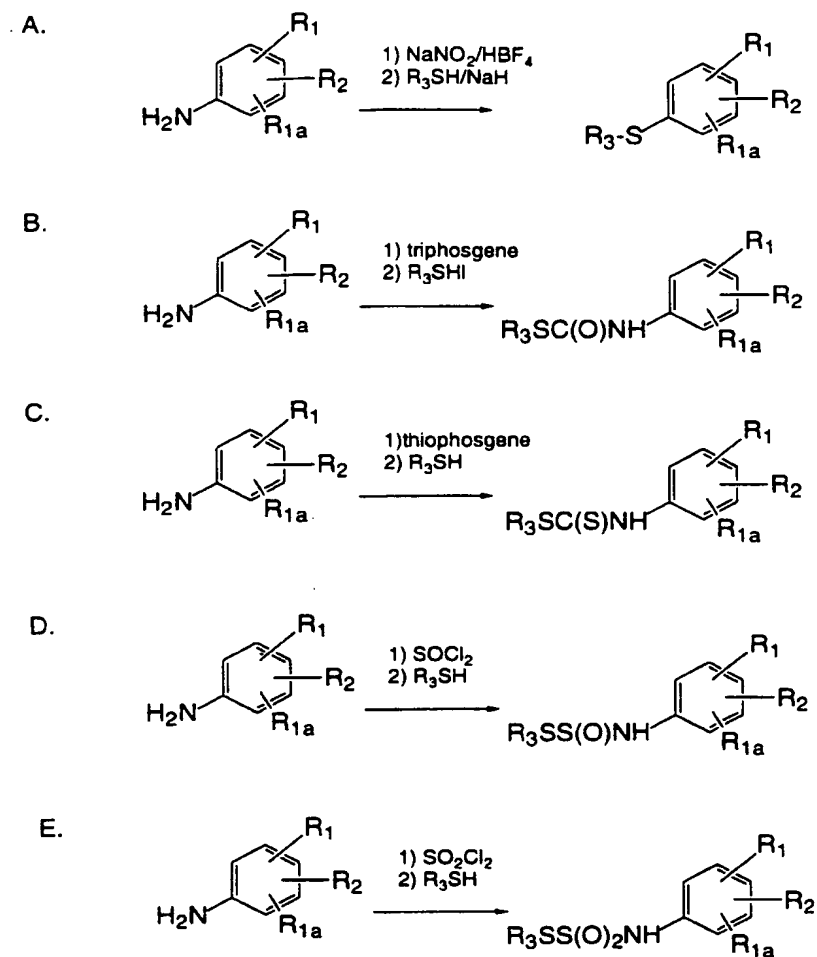
SCHEME 6

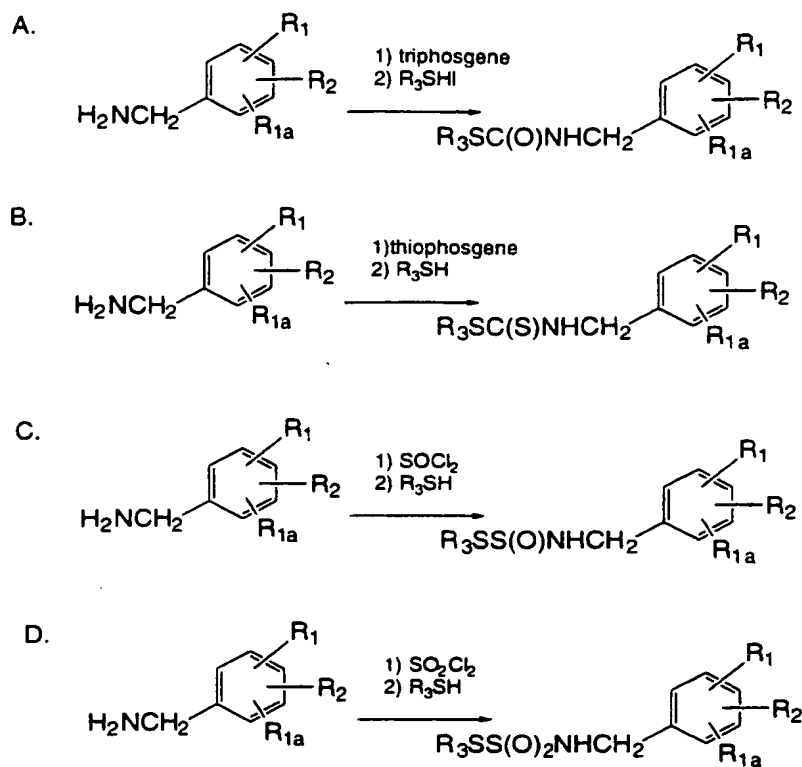
SCHEME 7

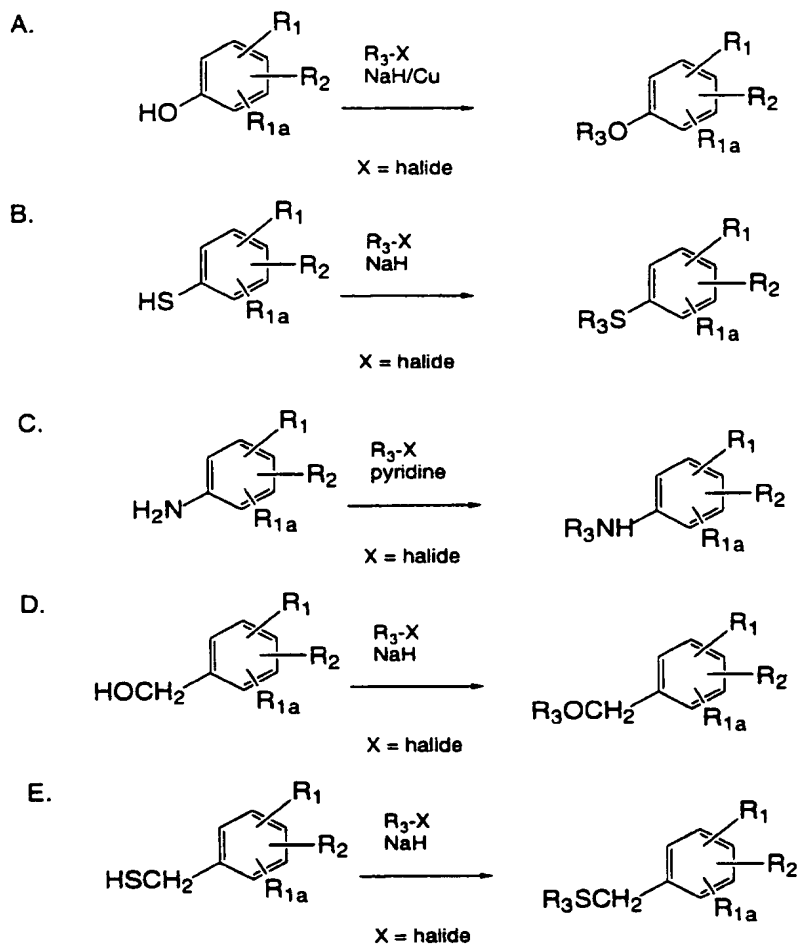
SCHEME 8

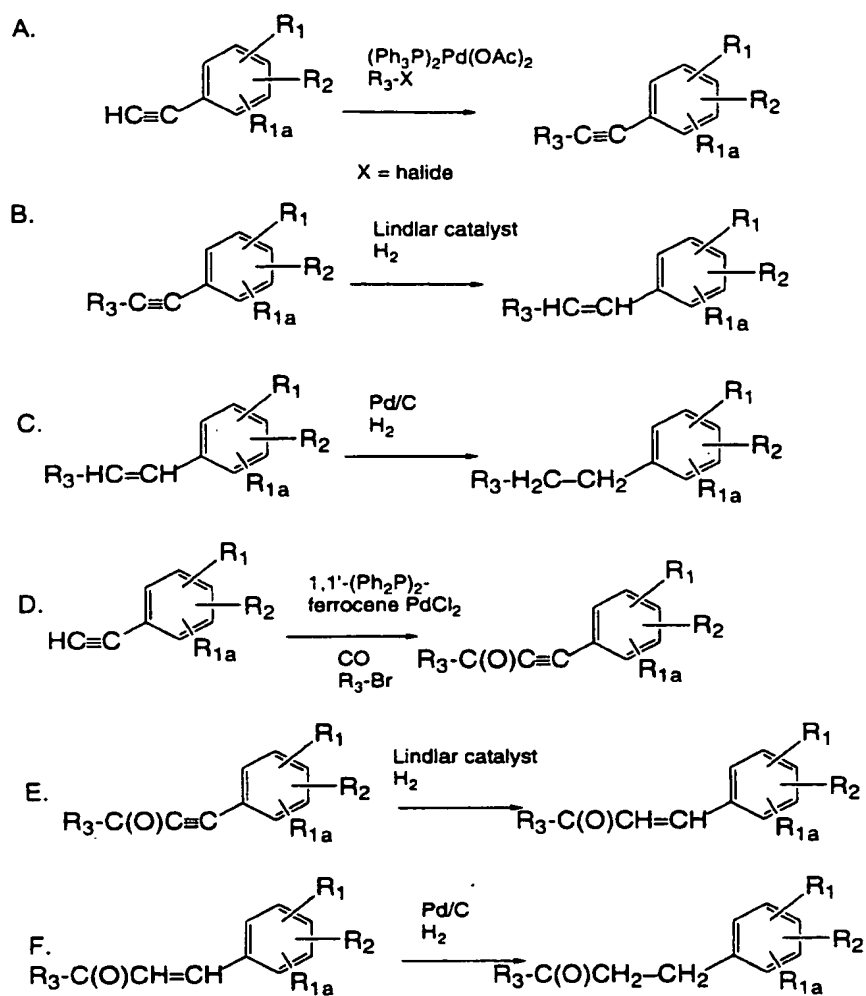
SCHEME 9

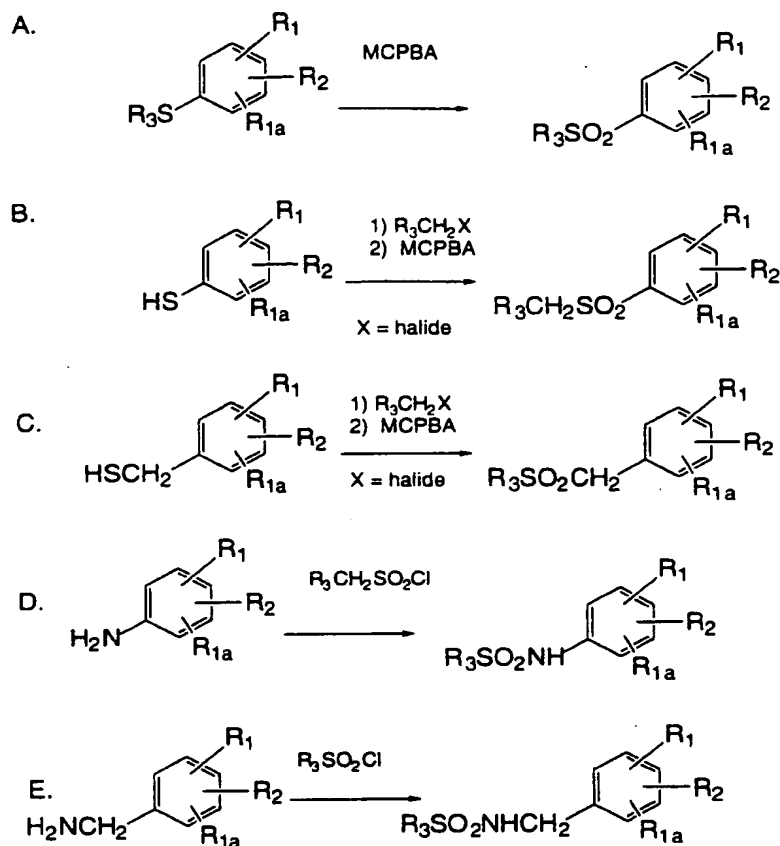
SCHEME 10

SCHEME 11

SCHEME 12

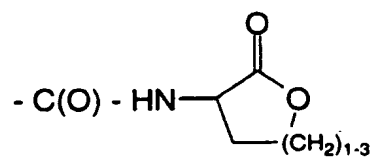
SCHEME 13

SCHEME 14

SCHEME 15

1635

Scheme 16 illustrates an alternative method for preparing compounds wherein R_2 is $-C(O)NH-CH(R_{14})-C(O)OR_{15}$ or



1640 as defined above.

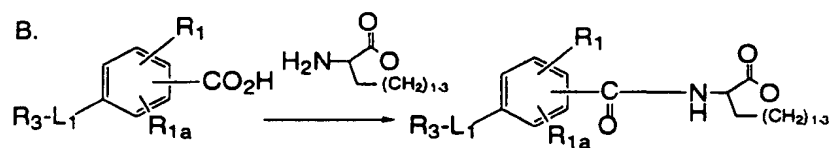
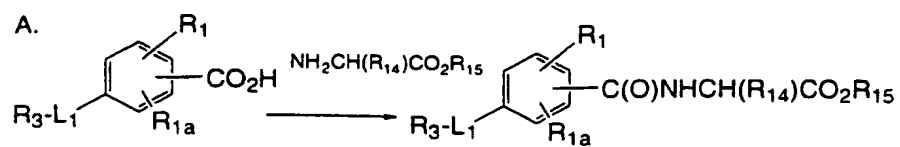
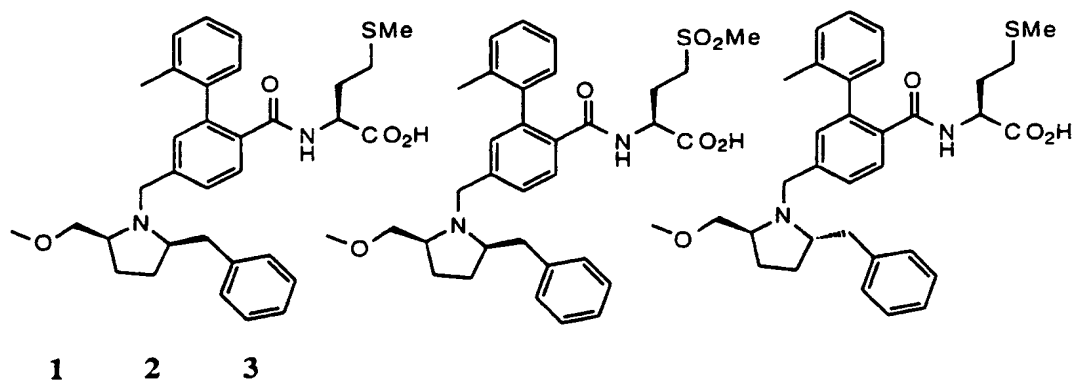
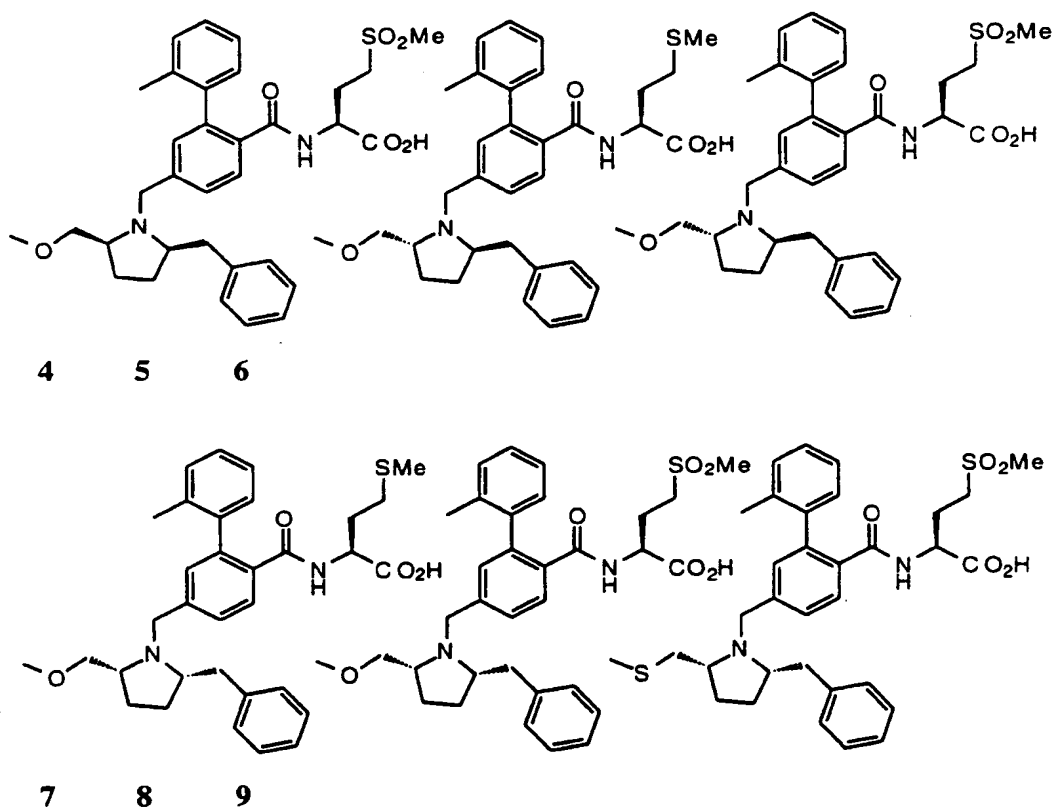
SCHEME 16

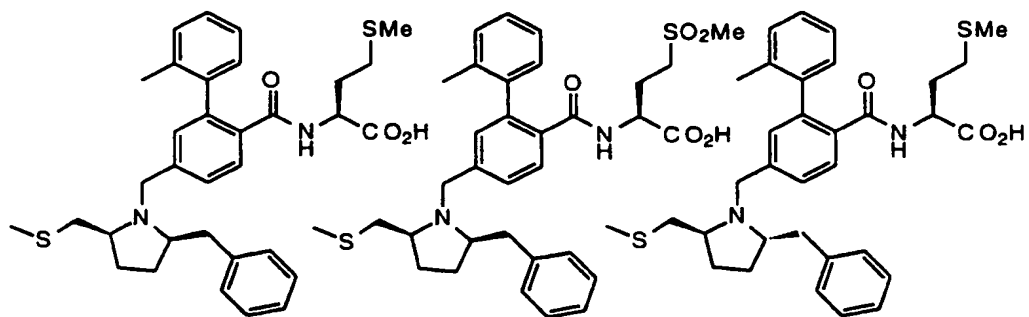
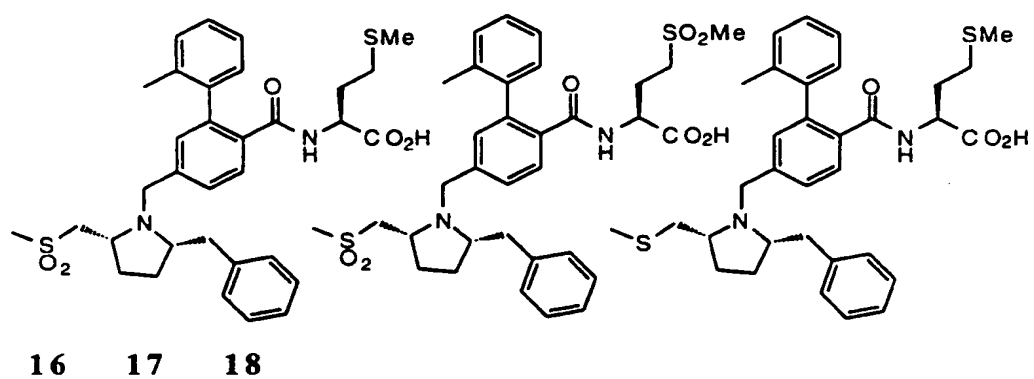
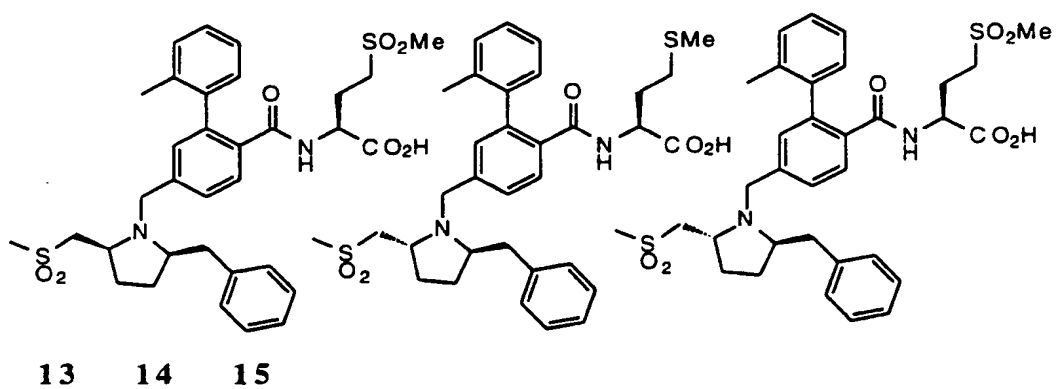
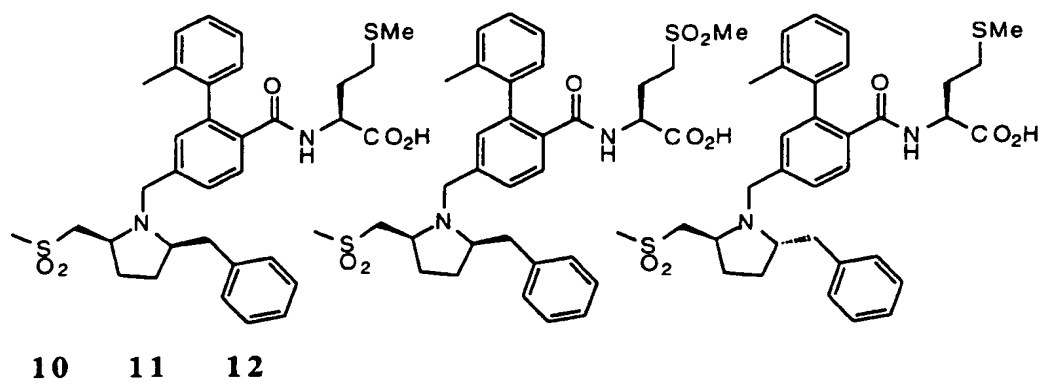
Table 6. Amines of the Type A(B)N-L₁

1645



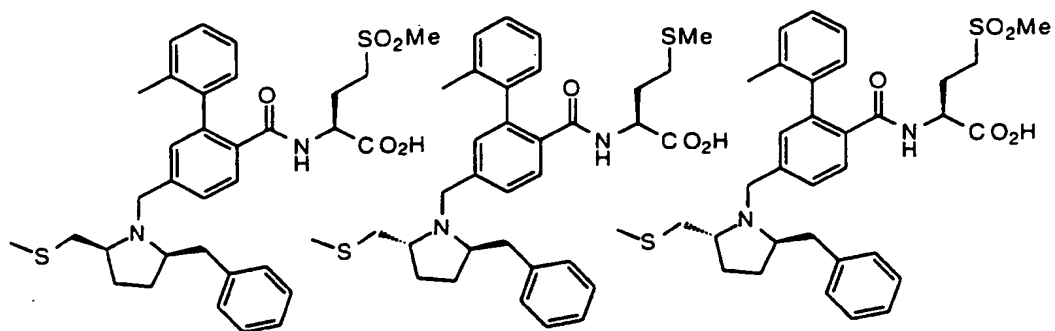
1650





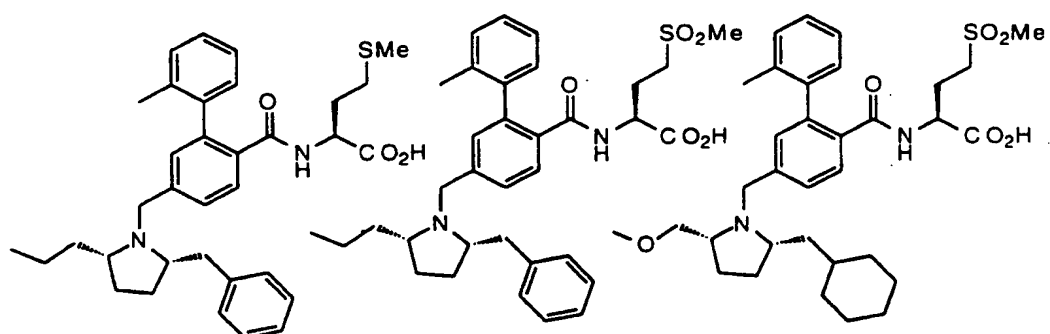
1665

19 20 21



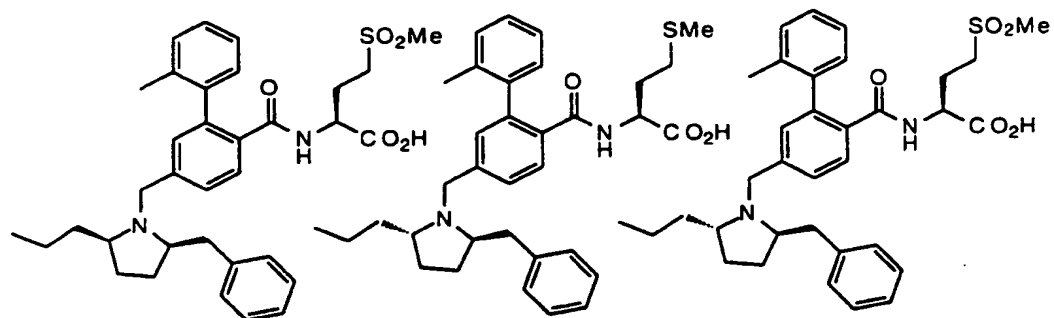
22 23 24

1670

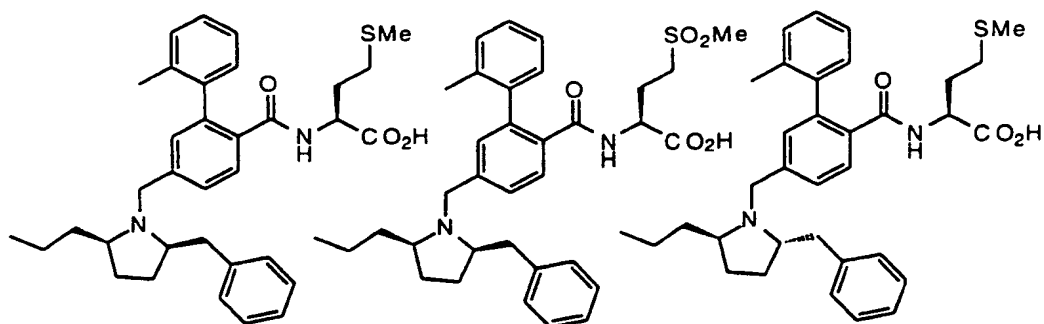


25 26 27

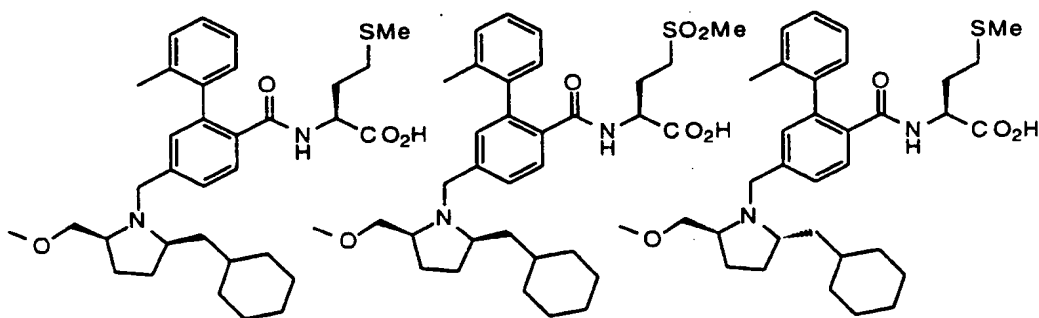
1675



28 29 30

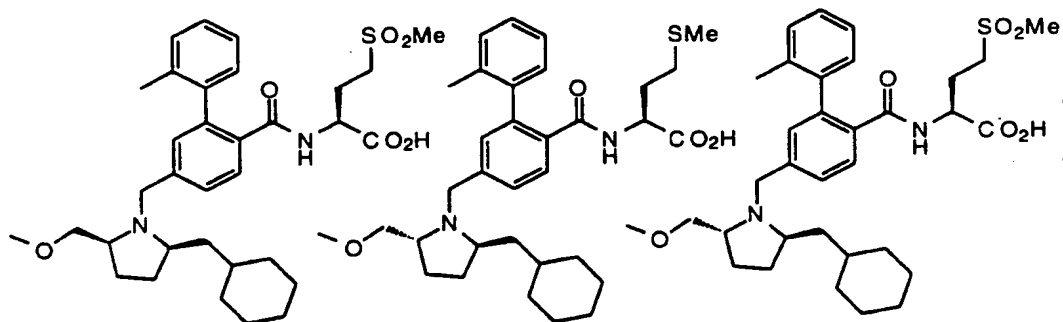


31 32 33

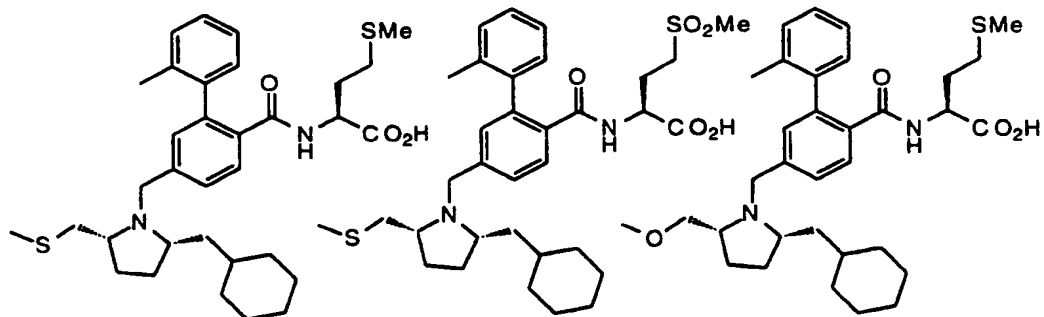


1680

34 35 36

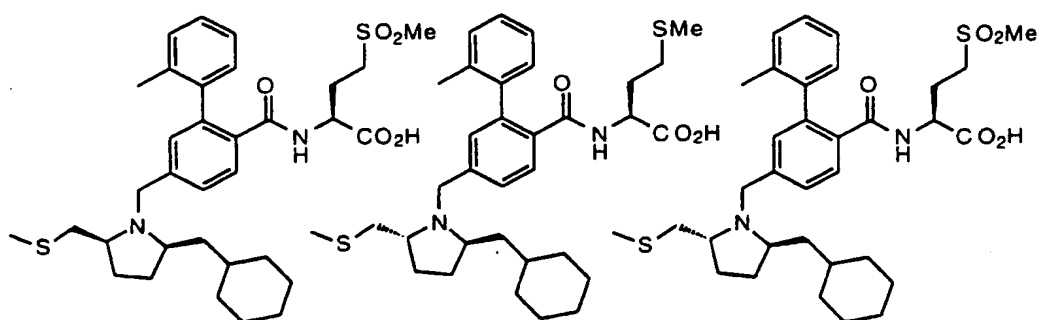


37 38 39

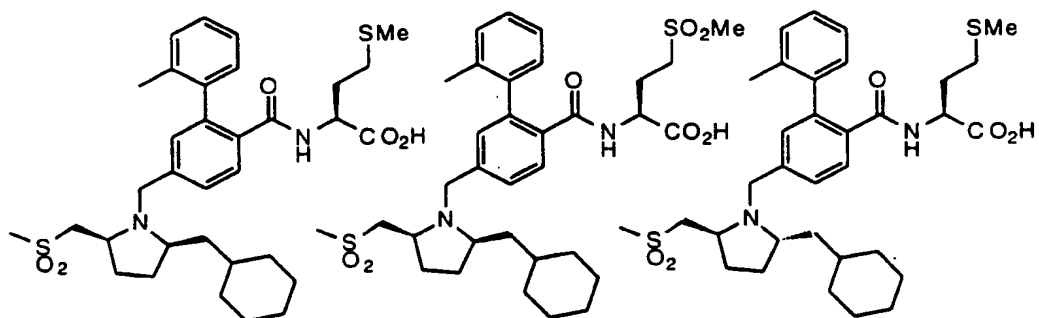


1685

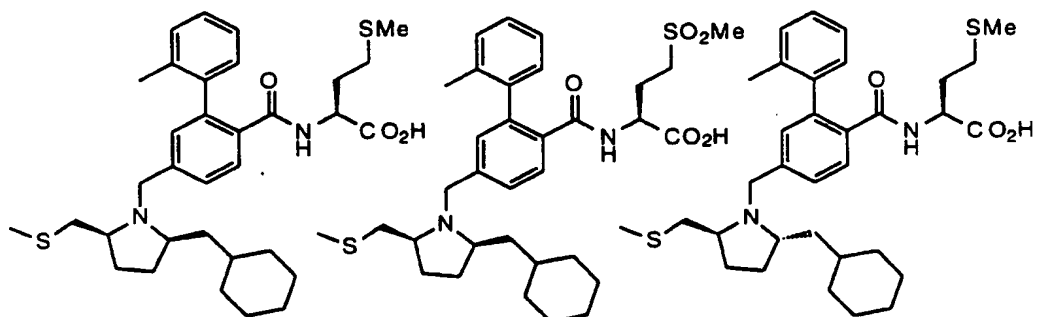
40 41 42



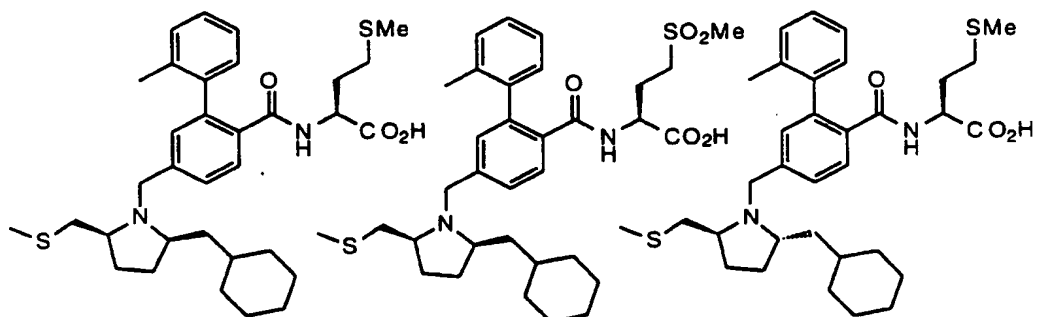
43 44 45

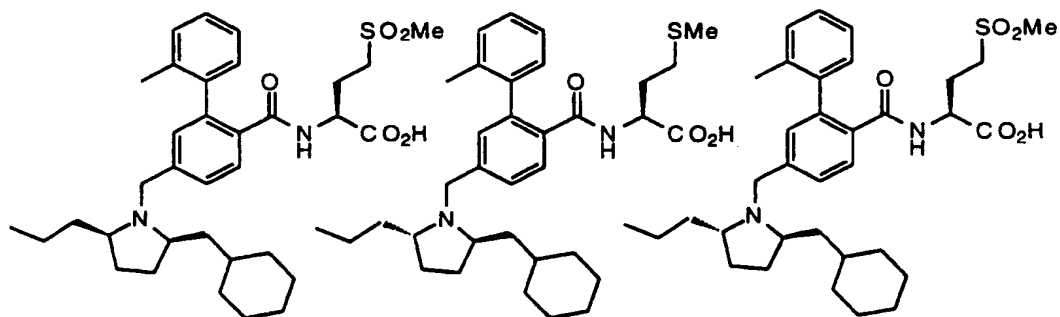
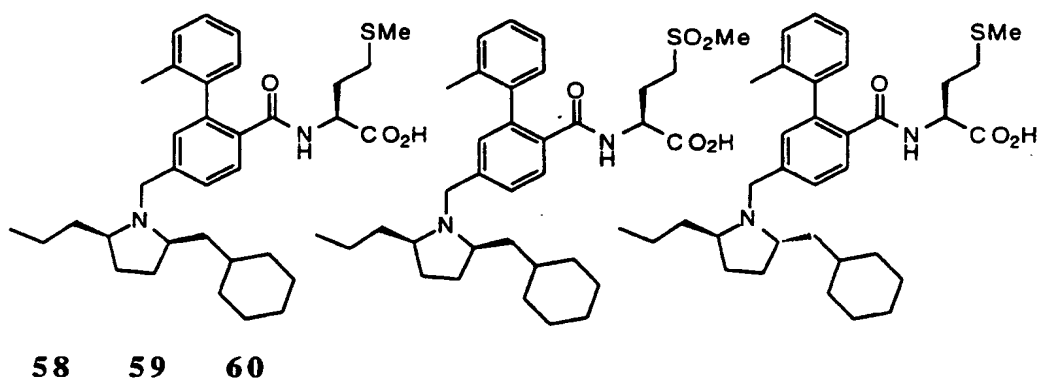
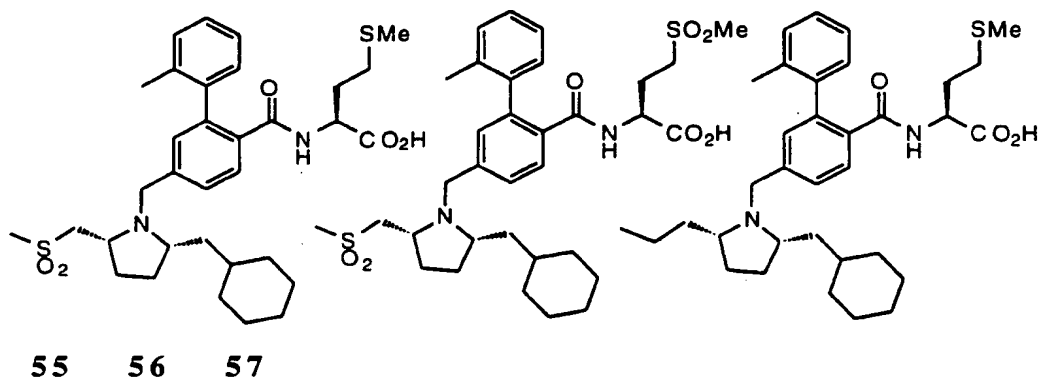
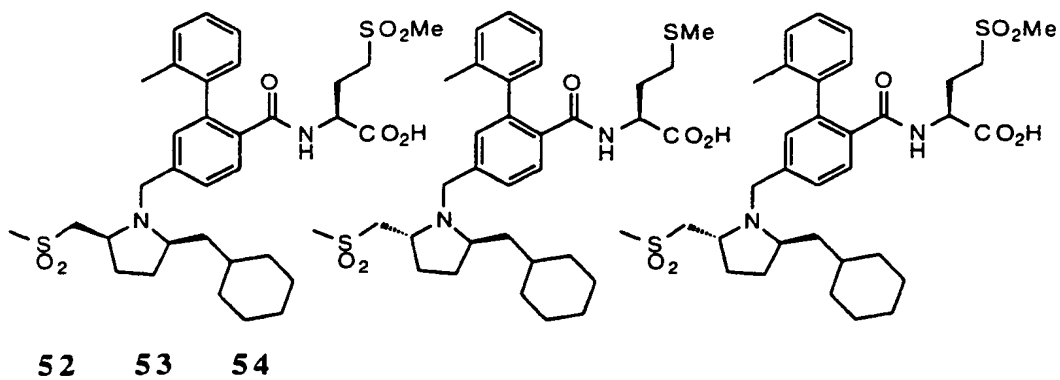


46 47 48

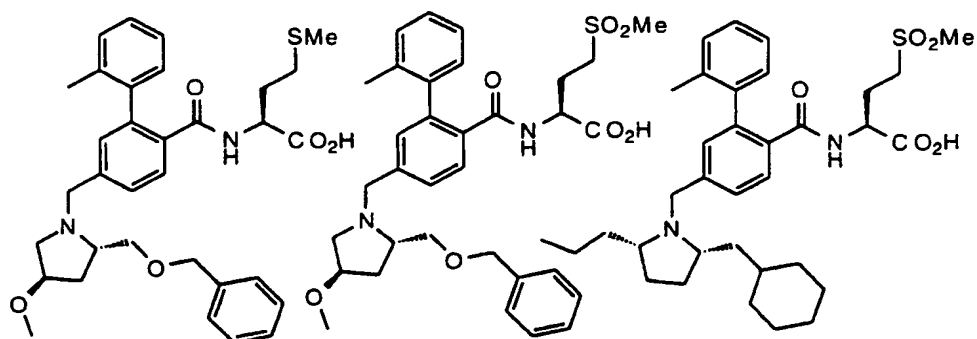


49 50 51



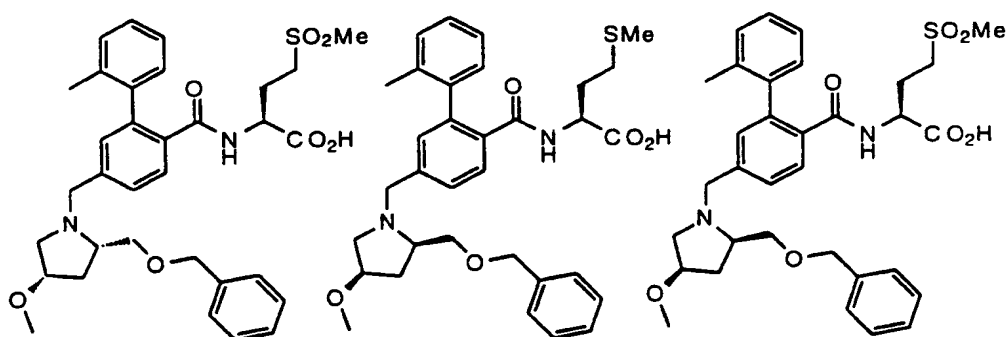


61 62 63

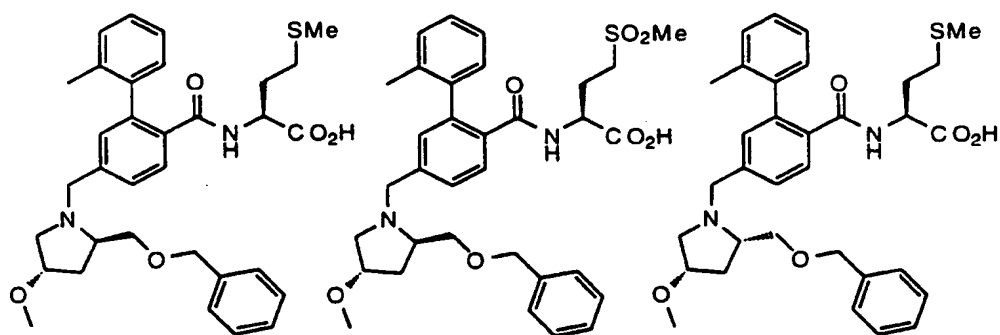


1710

64 65 66

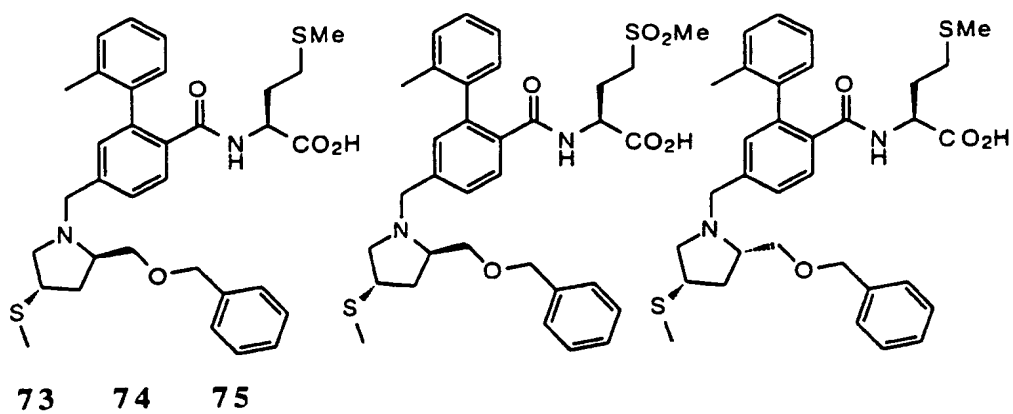


67 68 69

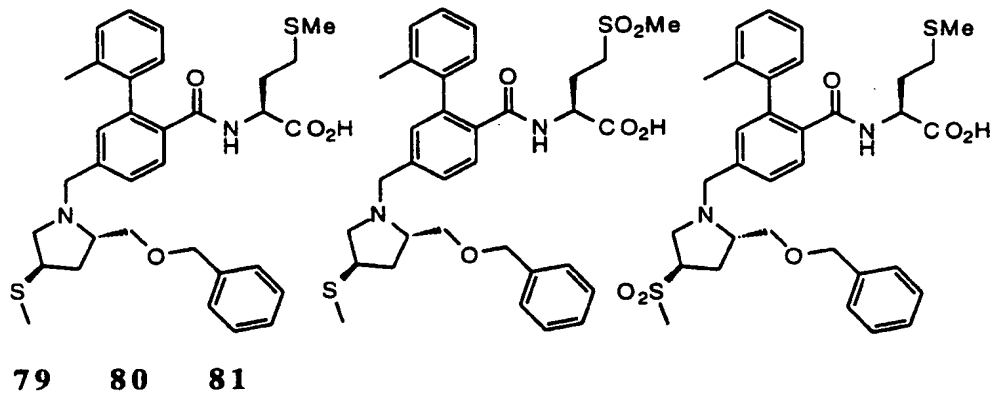
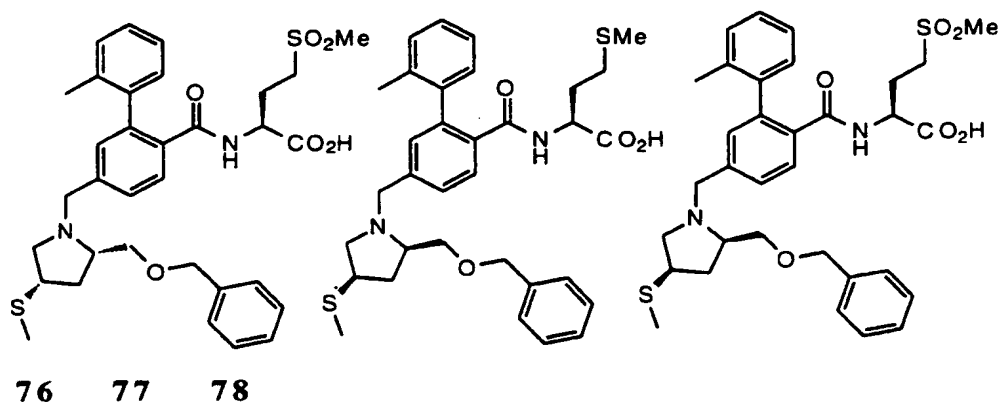


1715

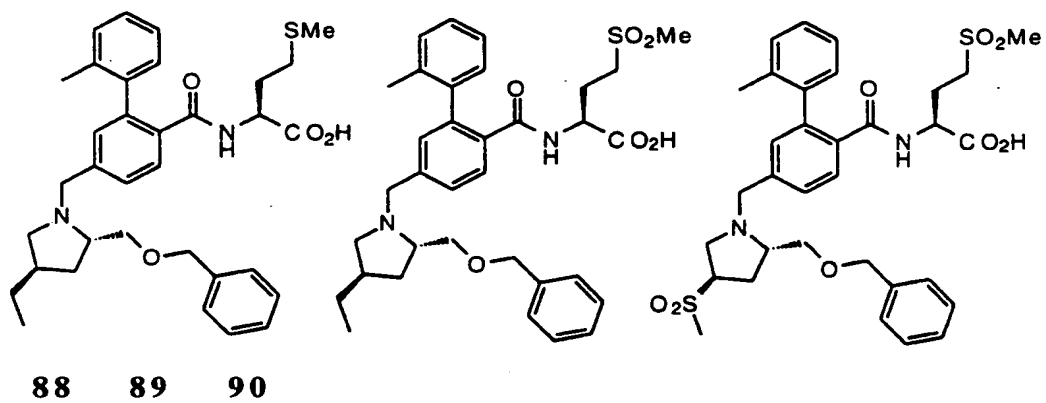
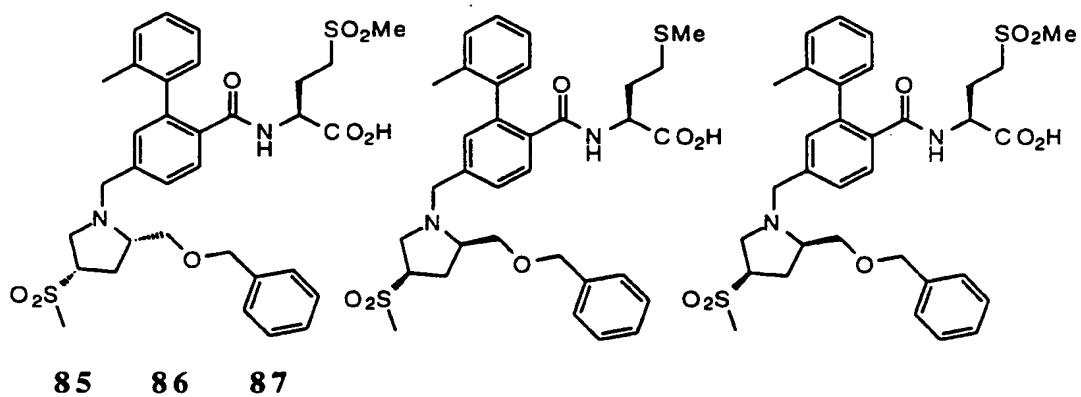
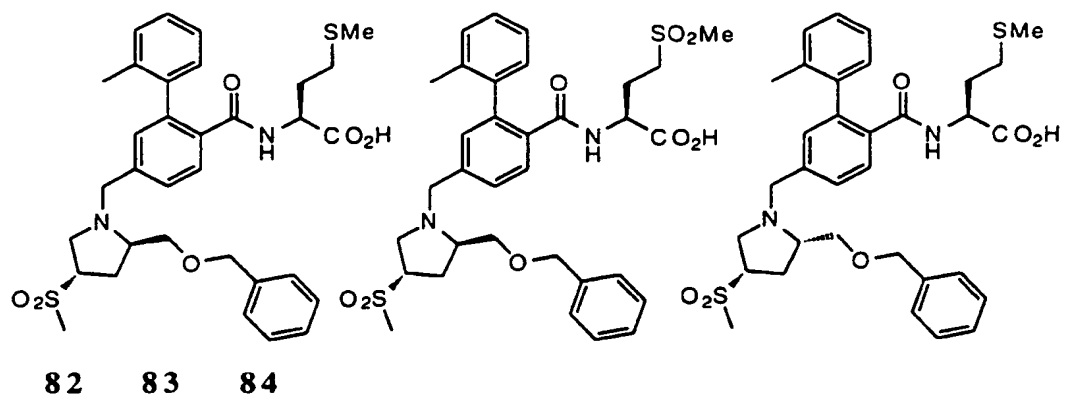
70 71 72

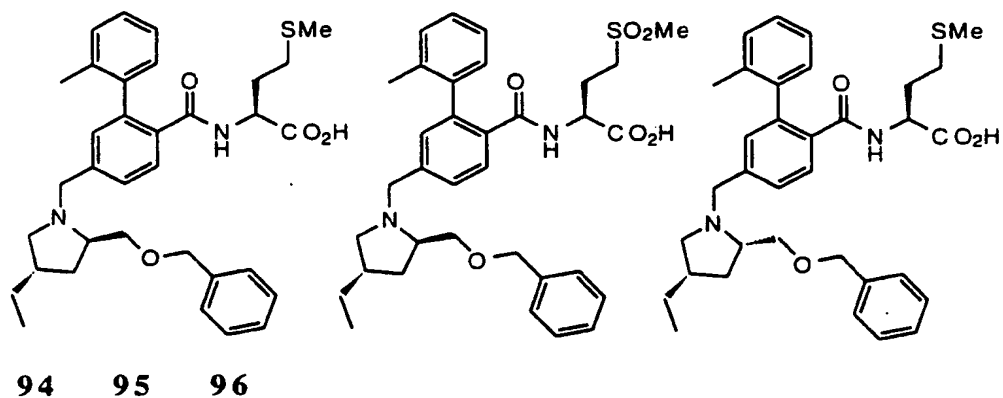
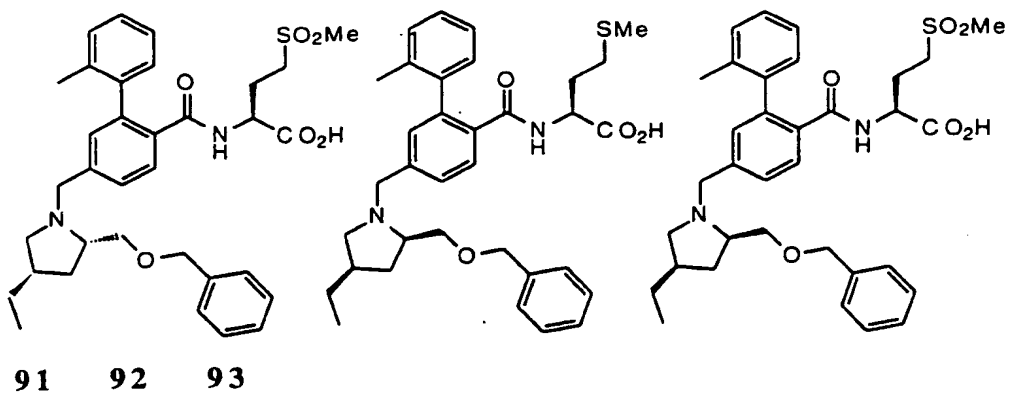


1720

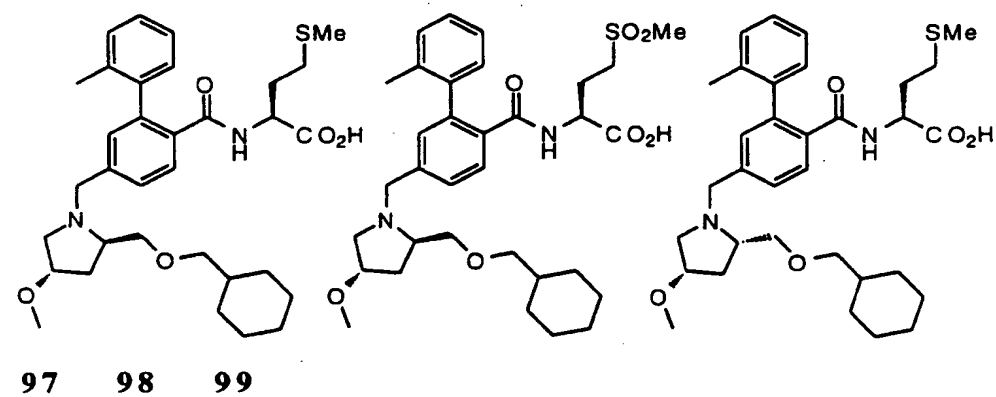


1725

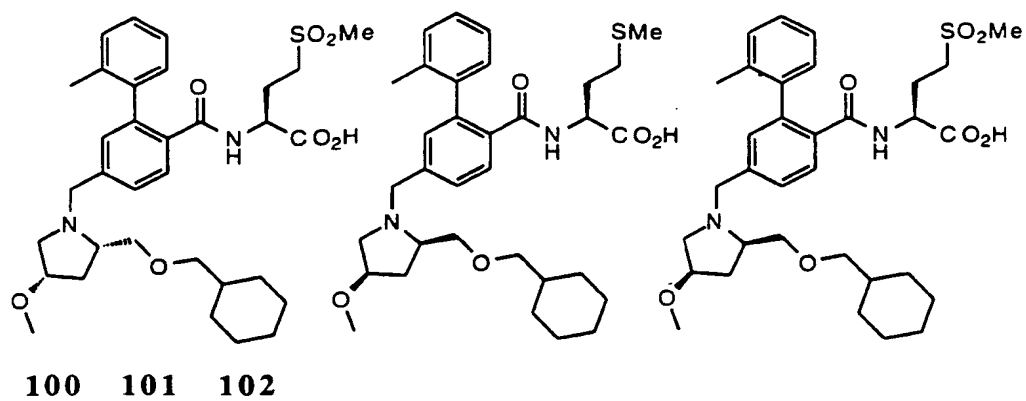




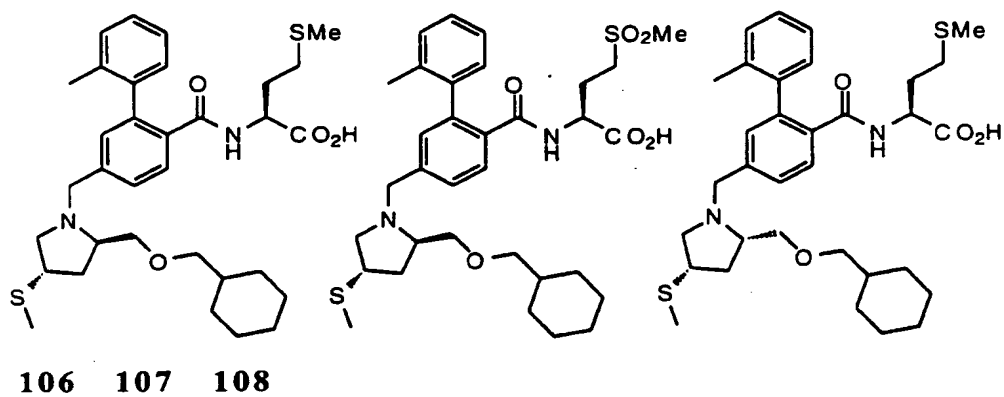
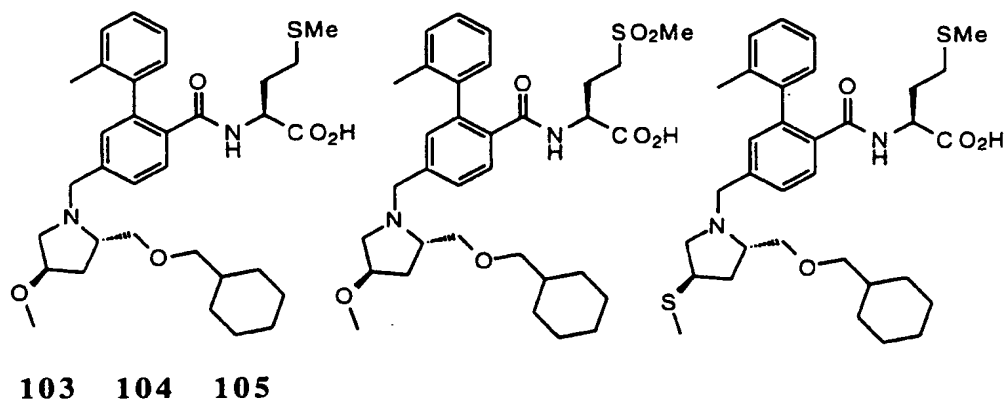
1740

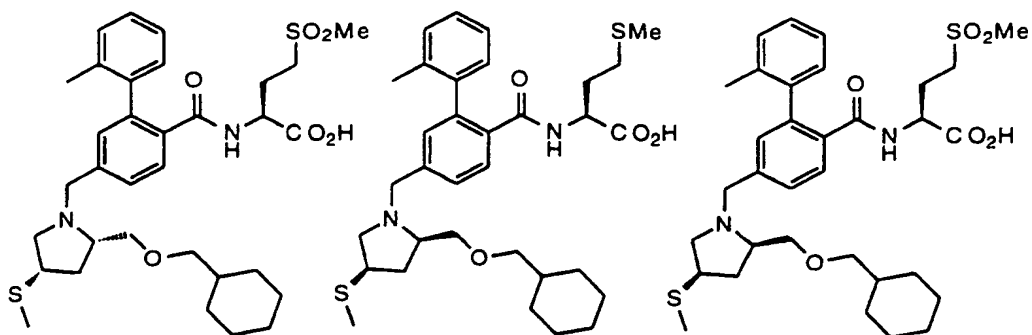


1745

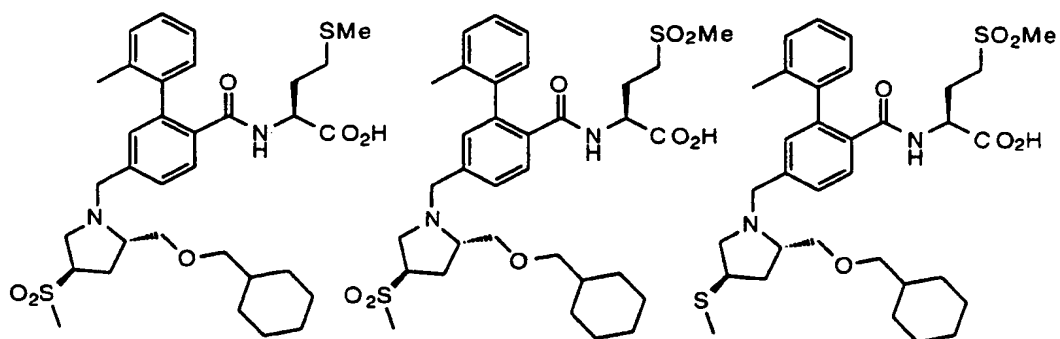
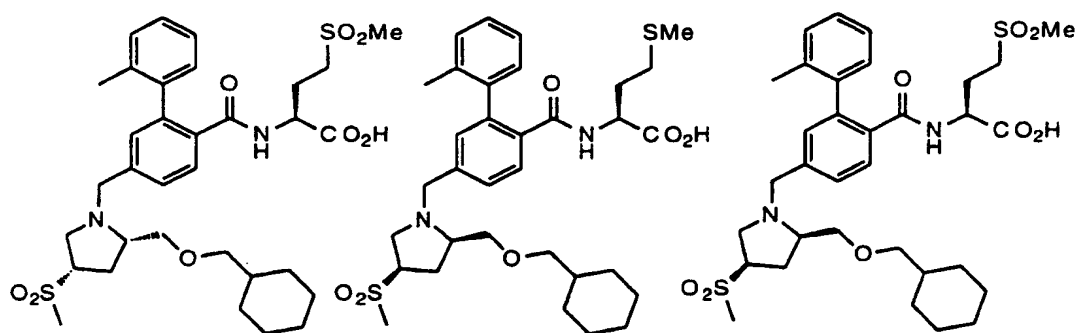


1750



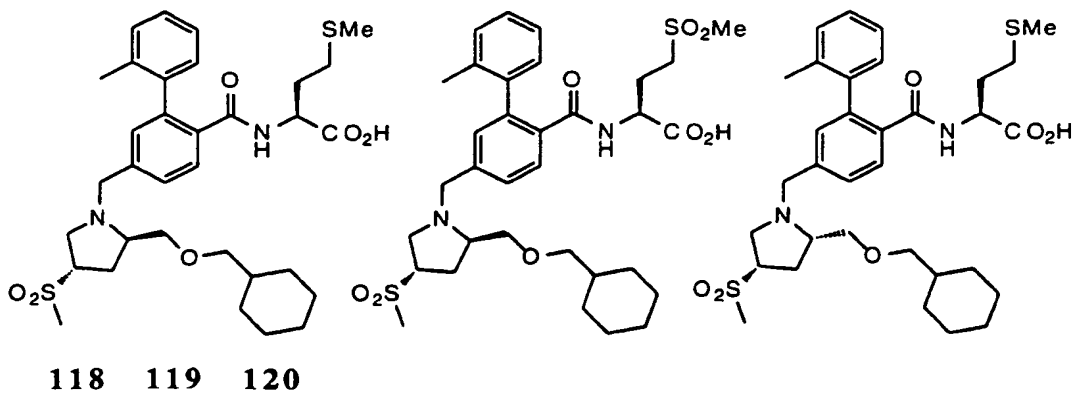


1755

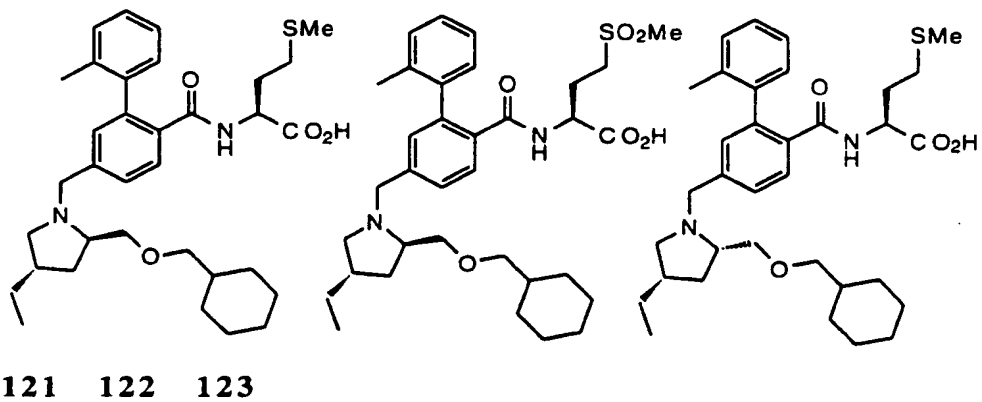
109 110 111**112 113 114**

1760

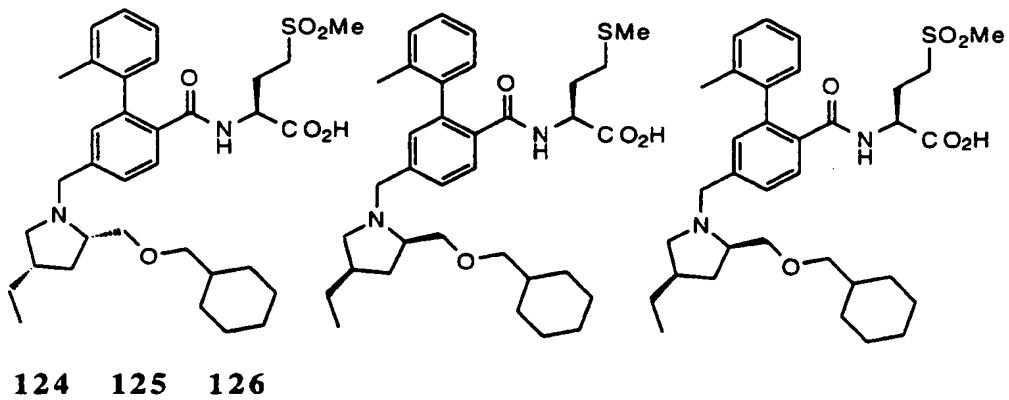
115 116 117



118 119 120

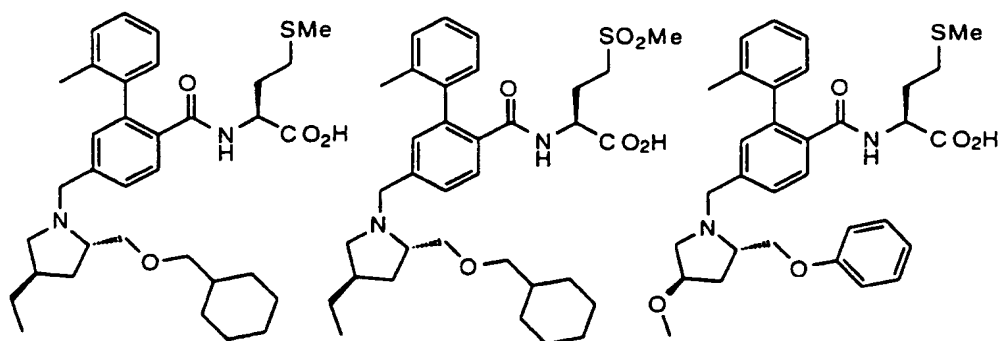


121 122 123

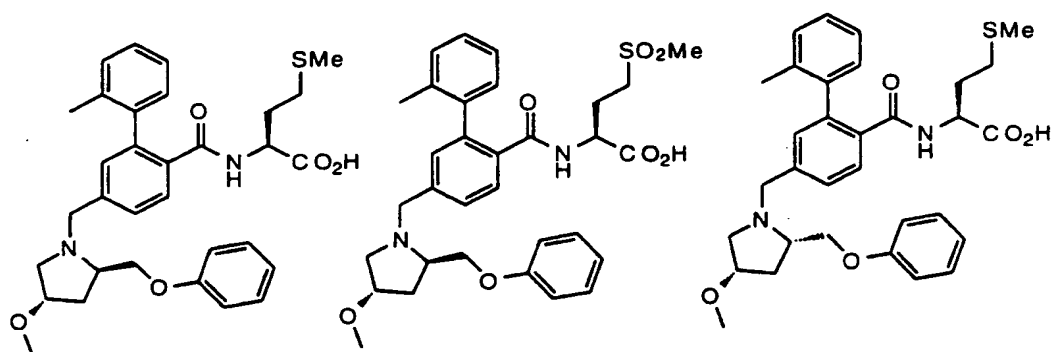


124 125 126

1770

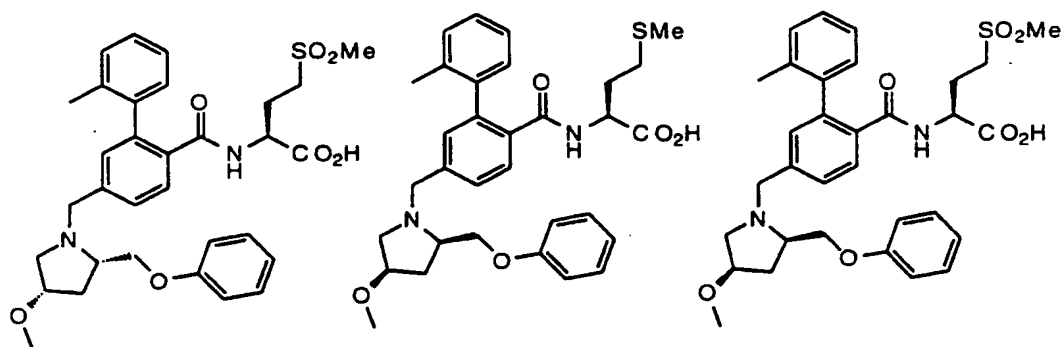


127 128 129

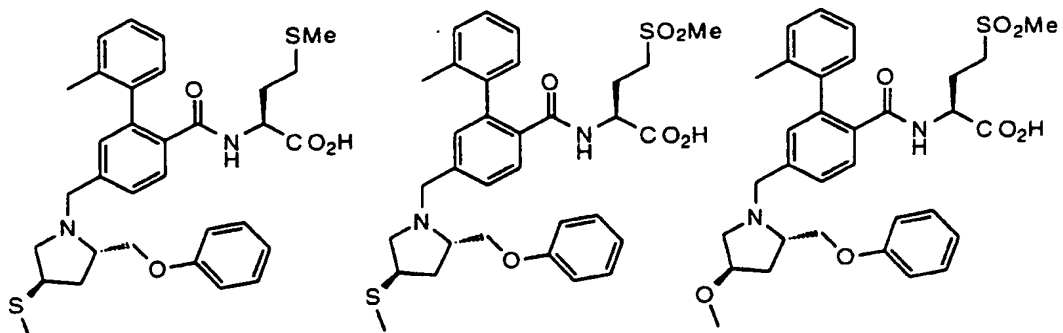


1775

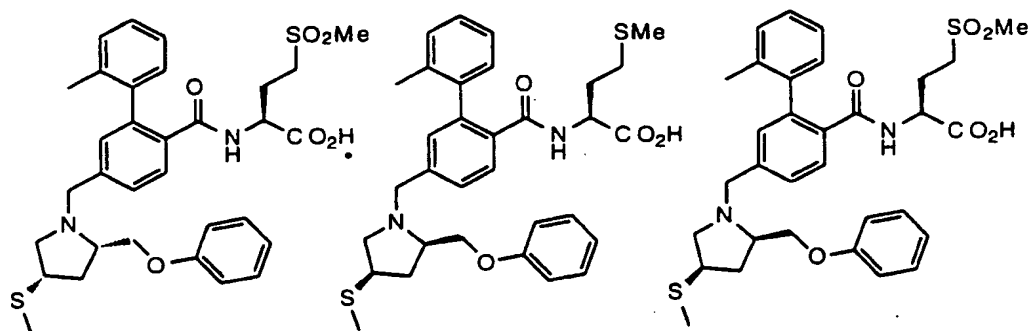
130 131 132



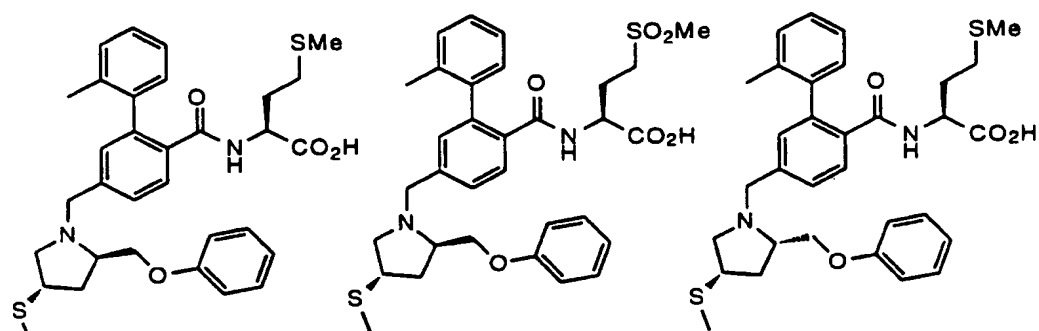
133 134 135

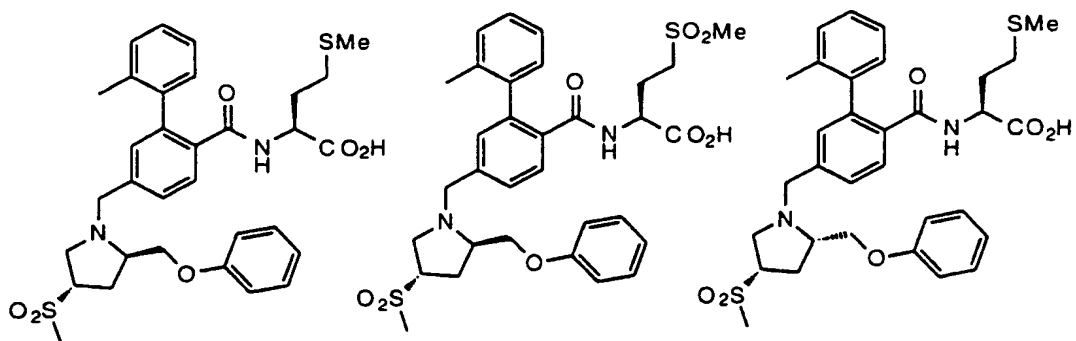


1780

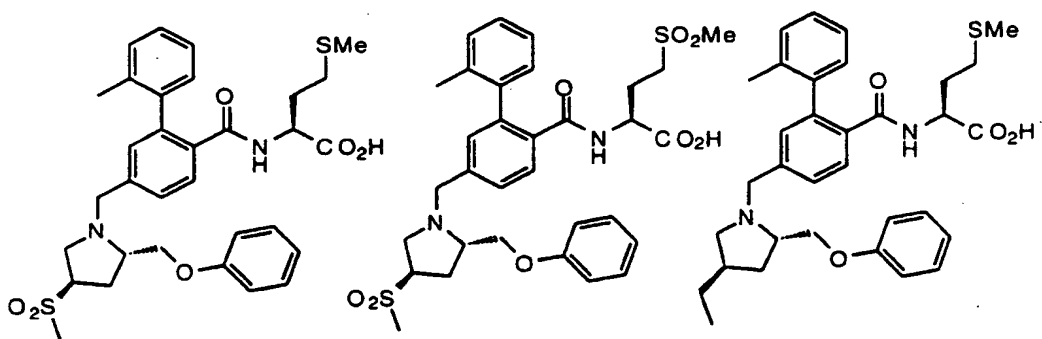
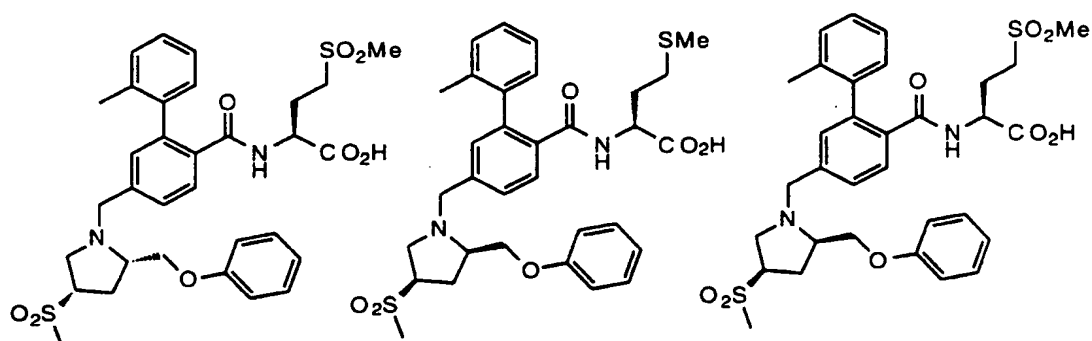


1785

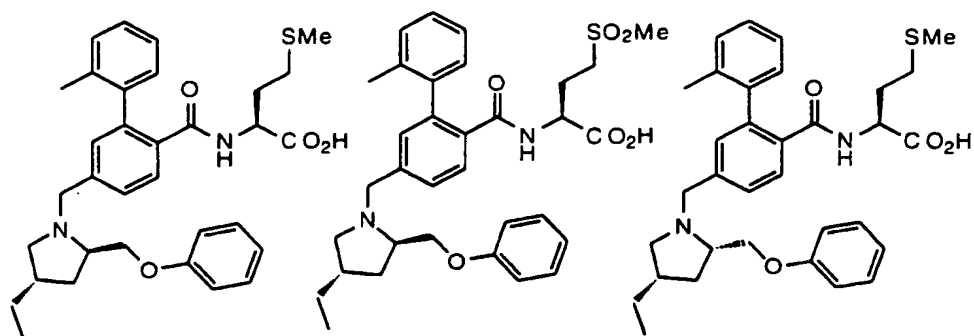




1790

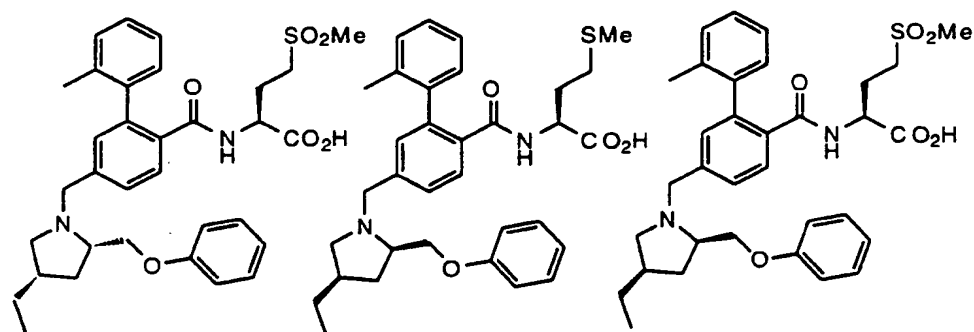


1795

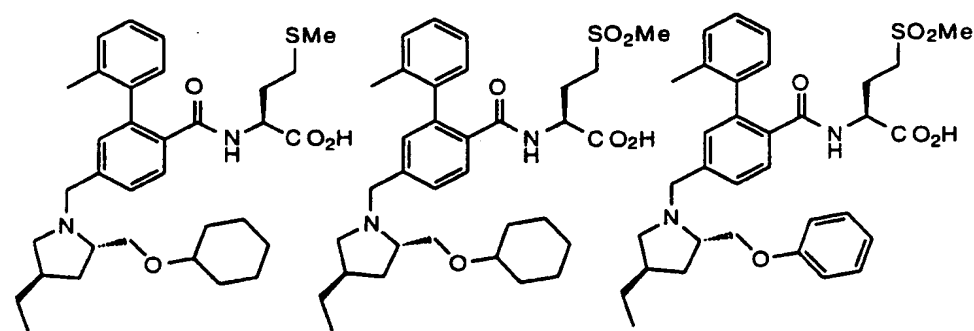


154 155 156

1800

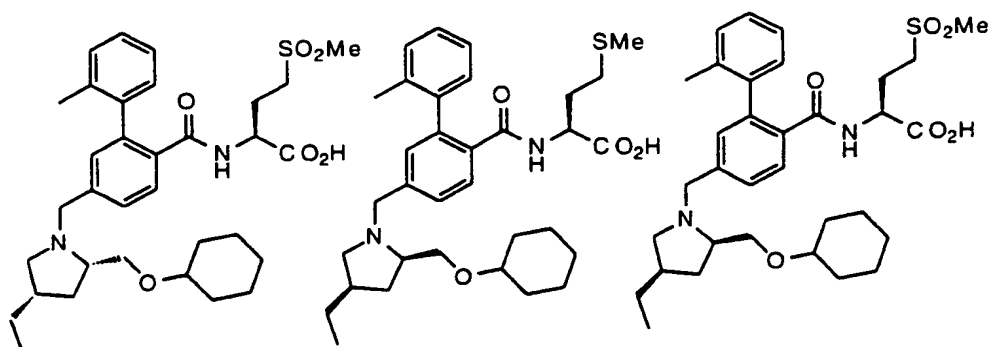
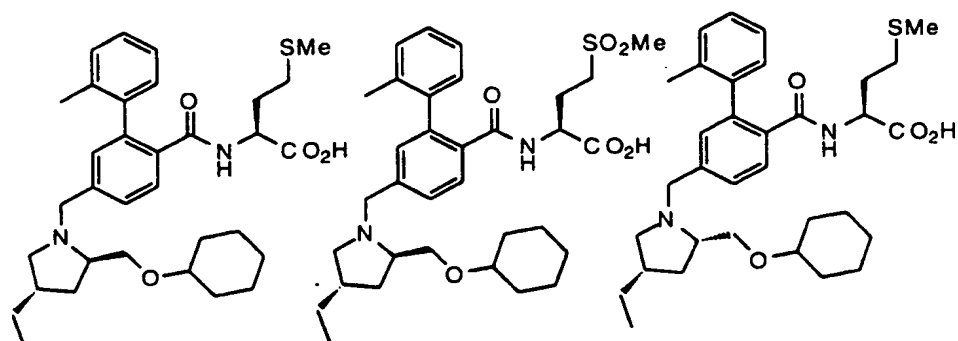
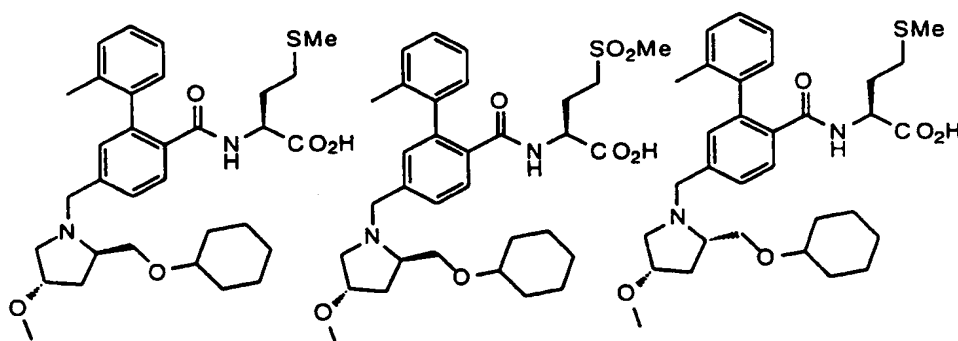


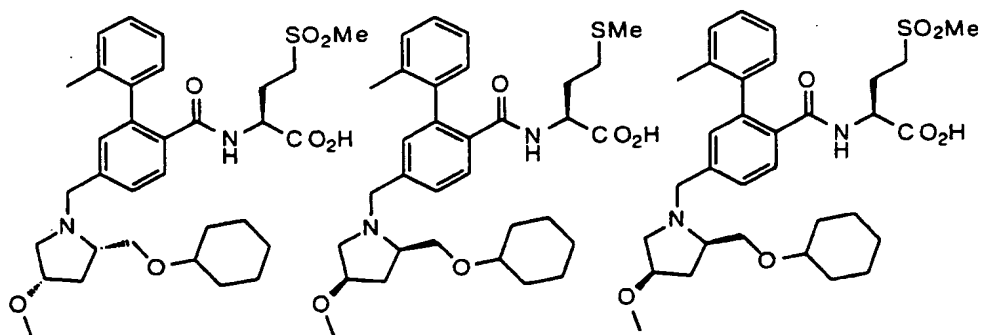
157 158 159



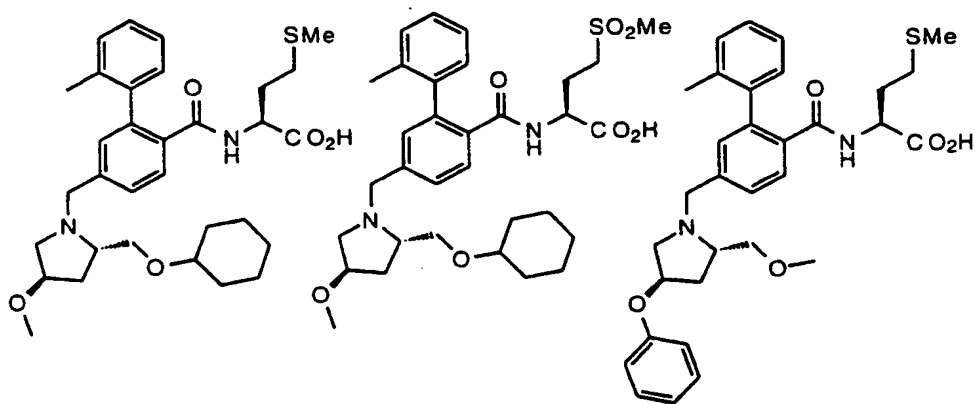
160 161 162

1805

**163 164 165****166 167 168****169 170 171**

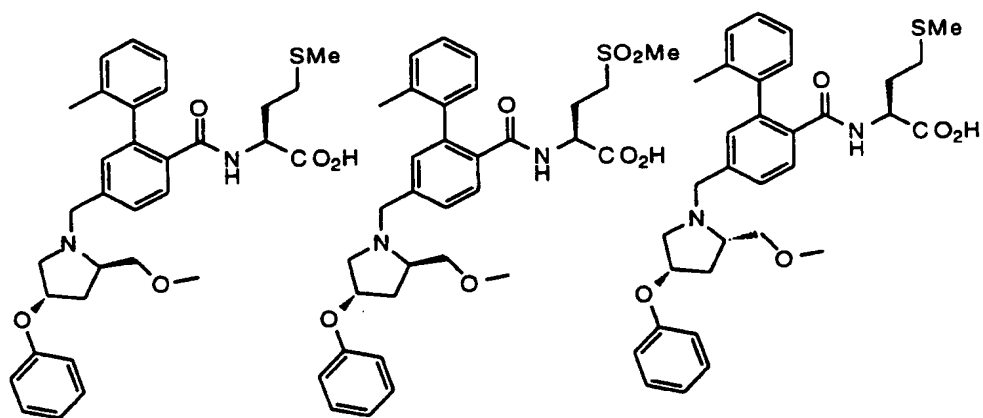


172 173 174

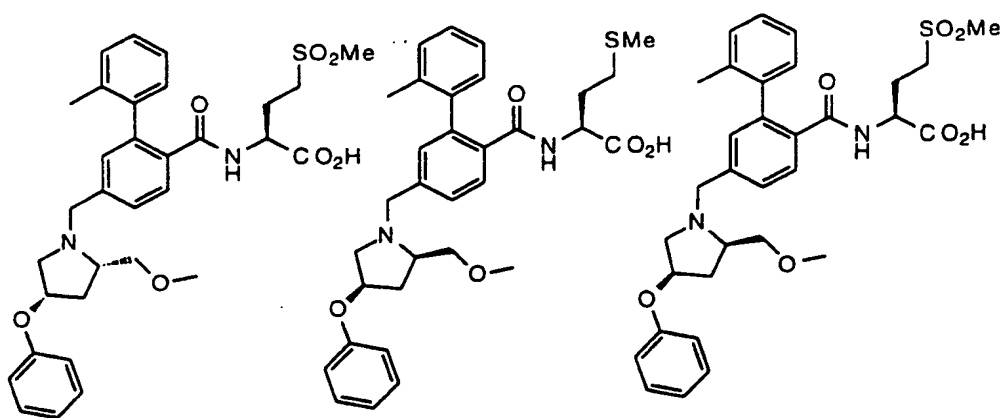


1820

175 176 177

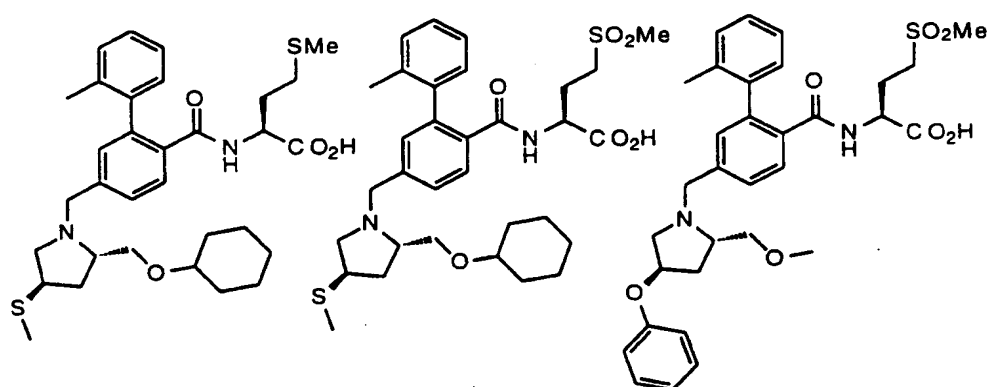


178 179 180



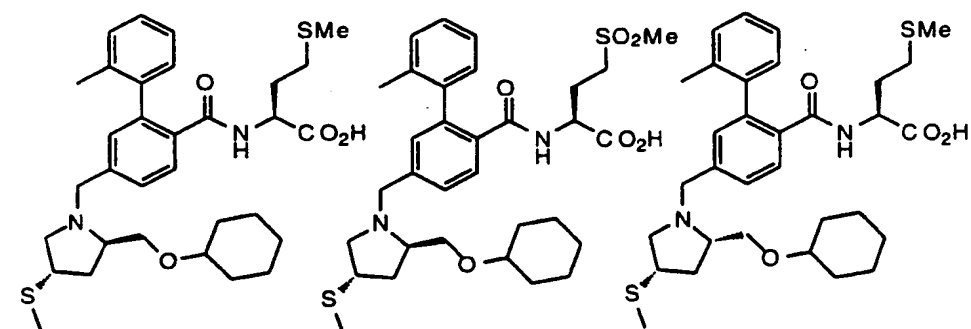
1825

181 182 183

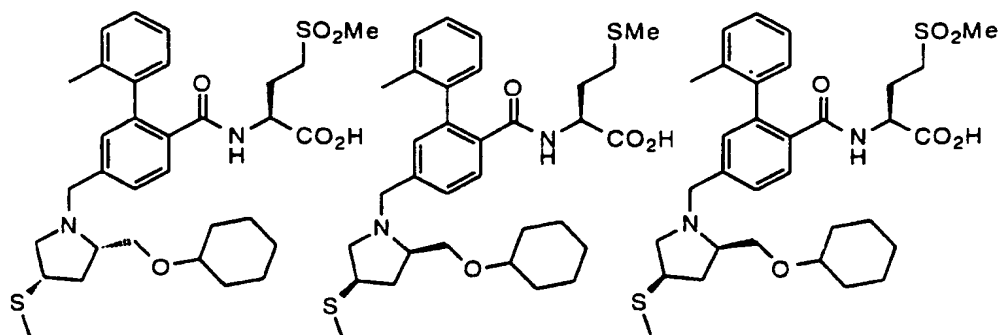


184 185 186

1830

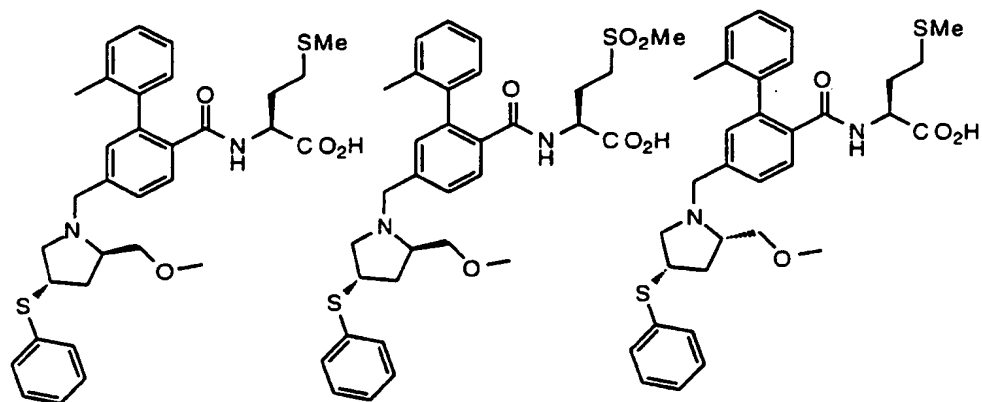


187 188 189

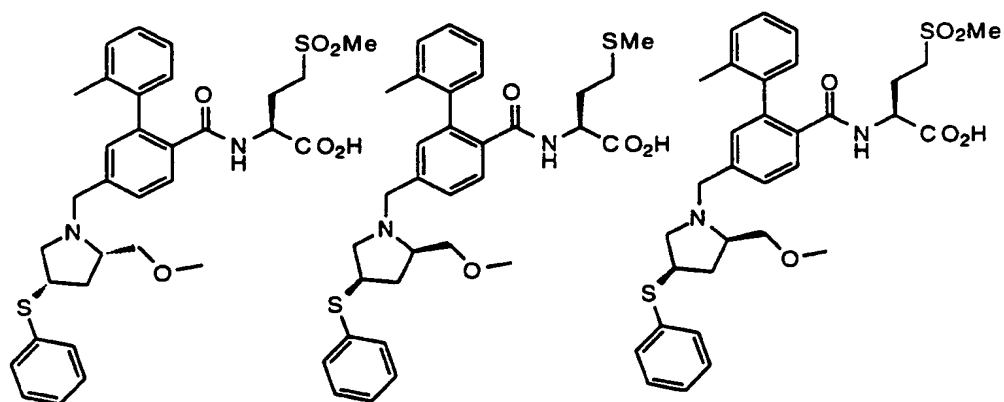


1835

190 191 192

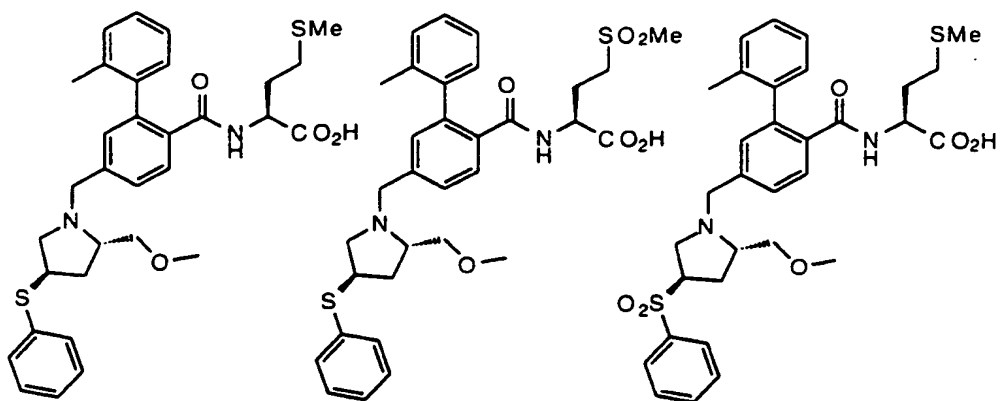


193 194 195



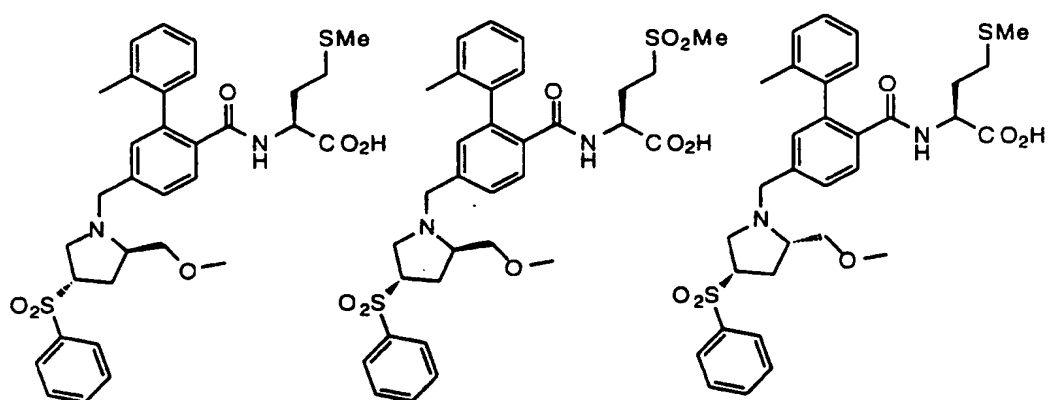
1840

196 197 198

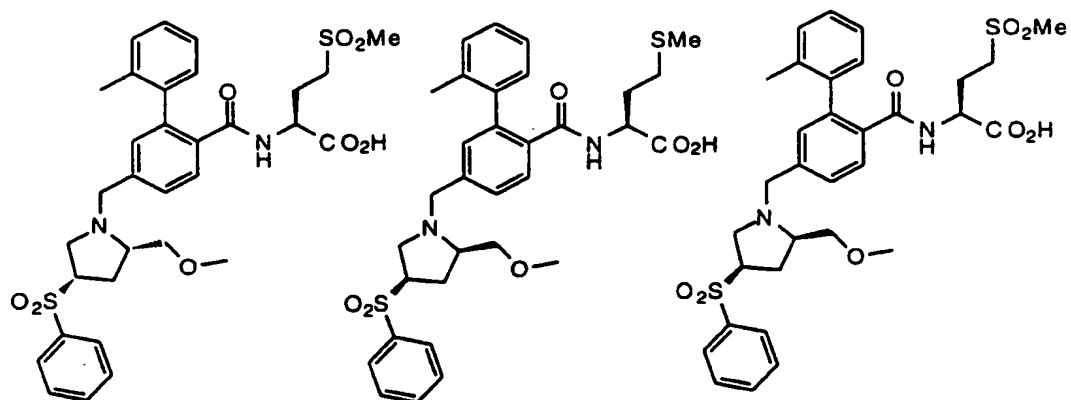


199 200 201

1845

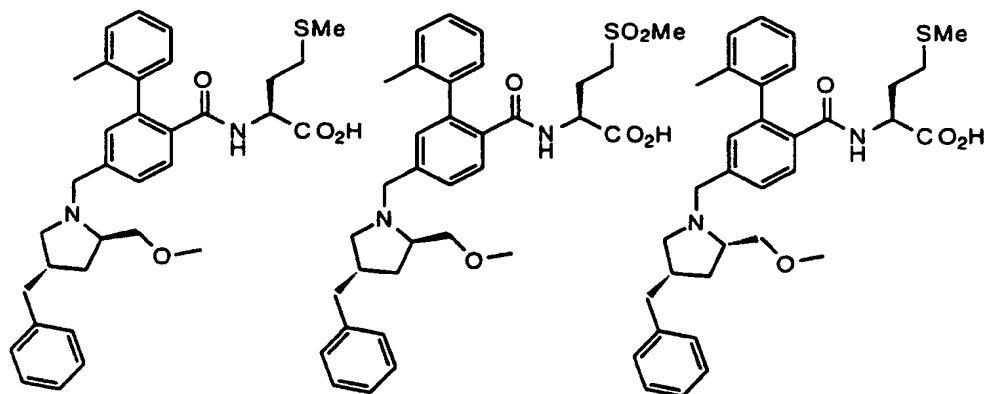
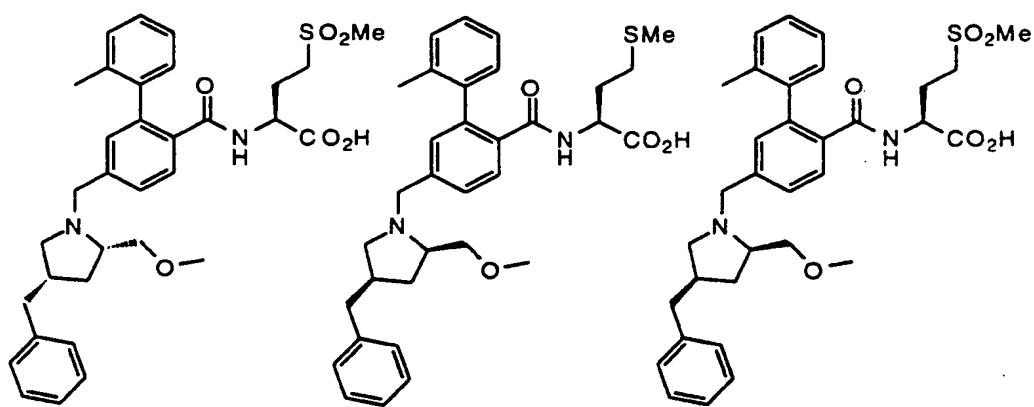
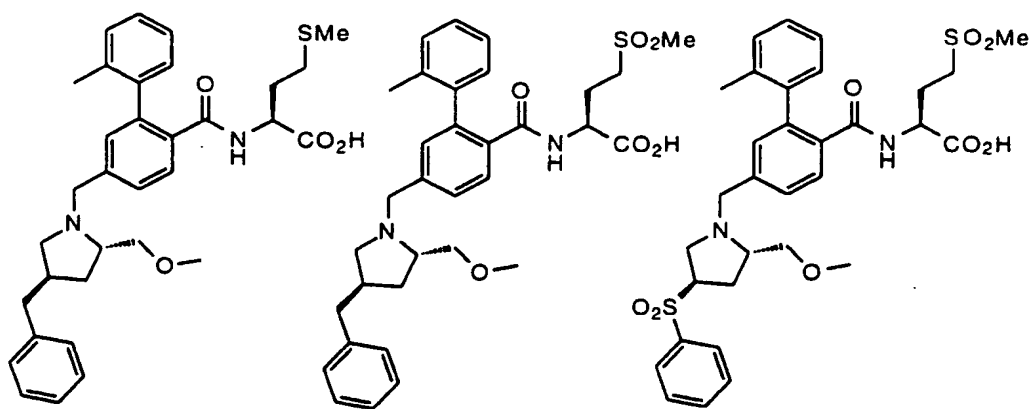


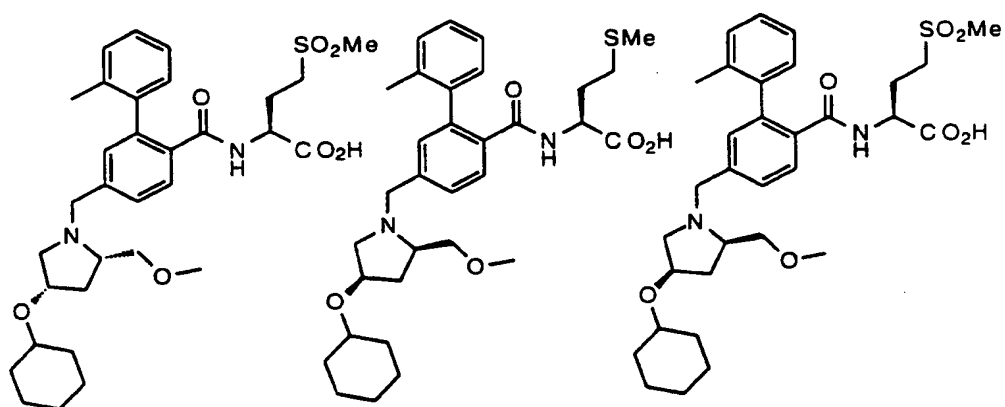
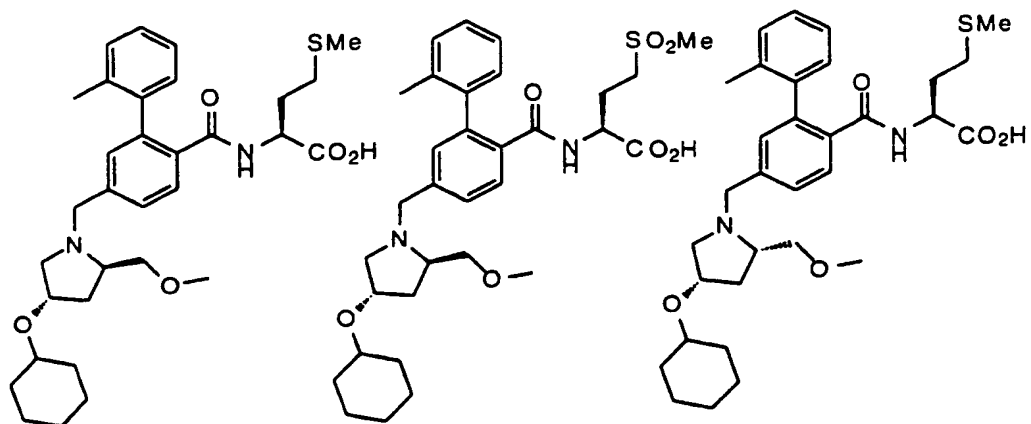
202 203 204



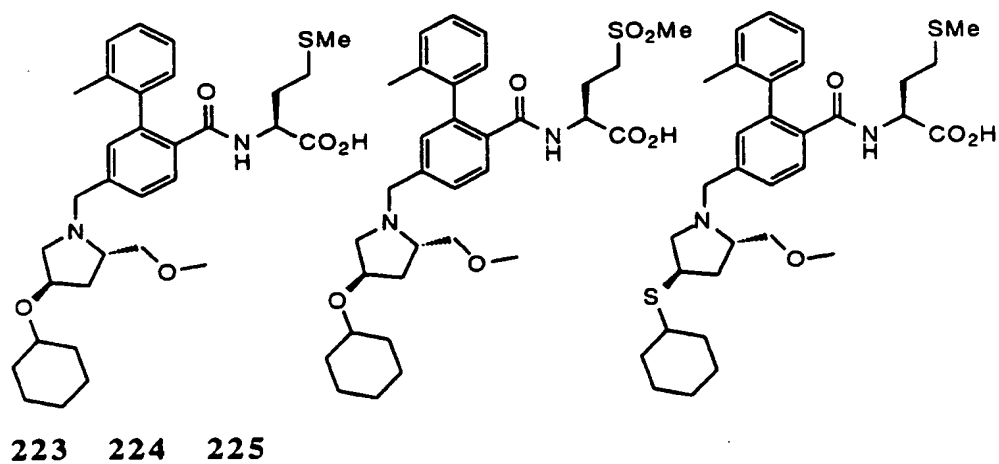
205 206 207

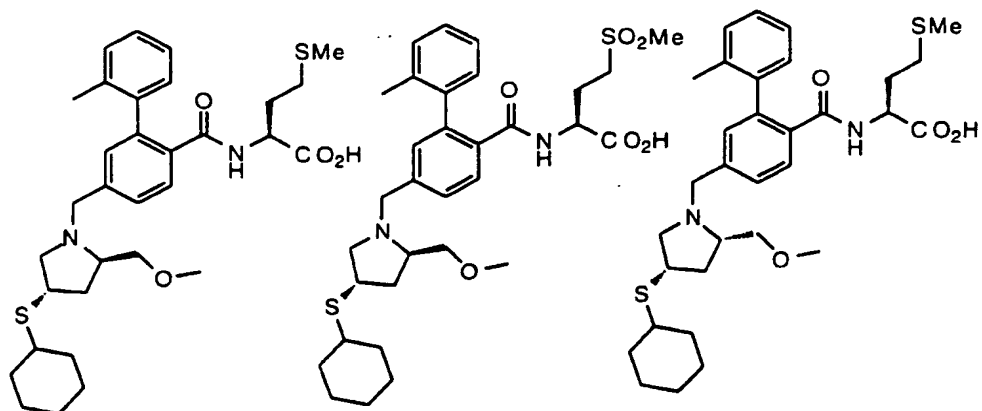
1850





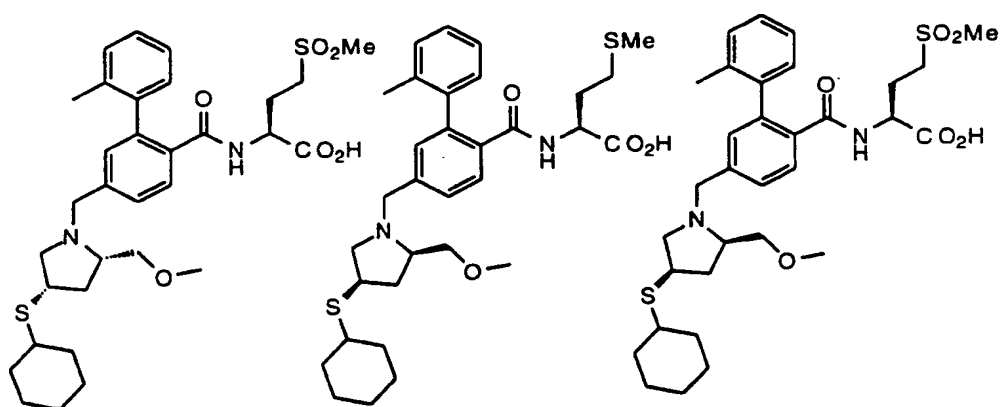
1865





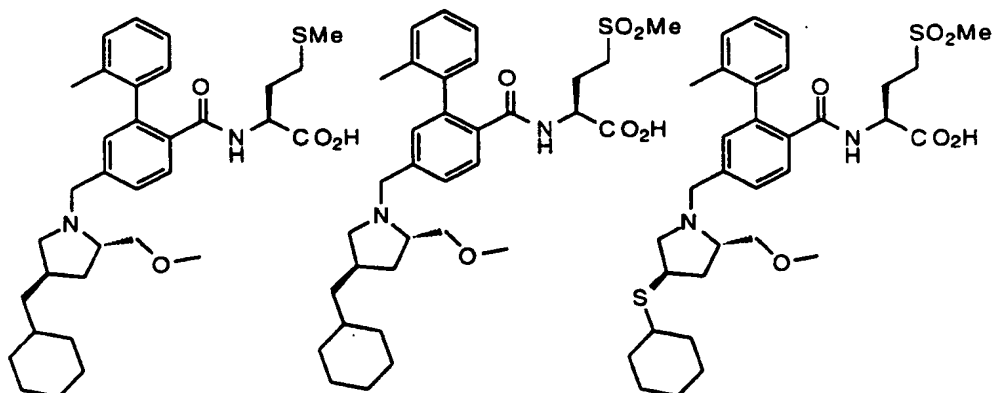
1870

226 227 228

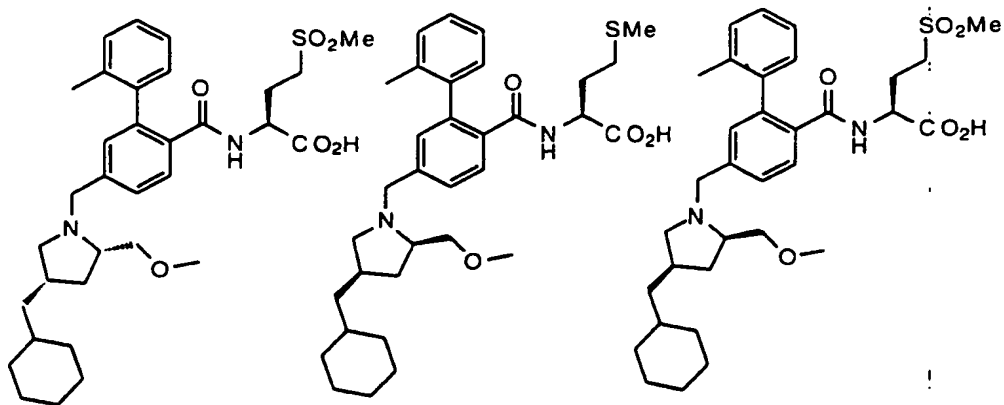


229 230 231

1875

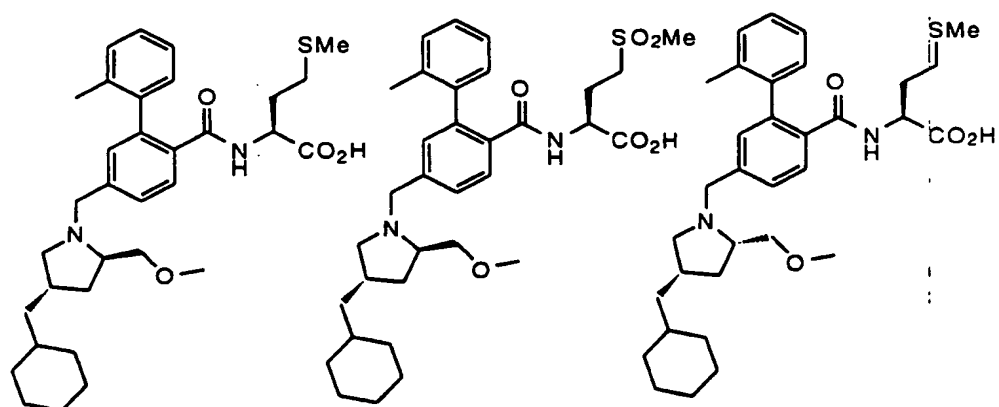


232 233 234

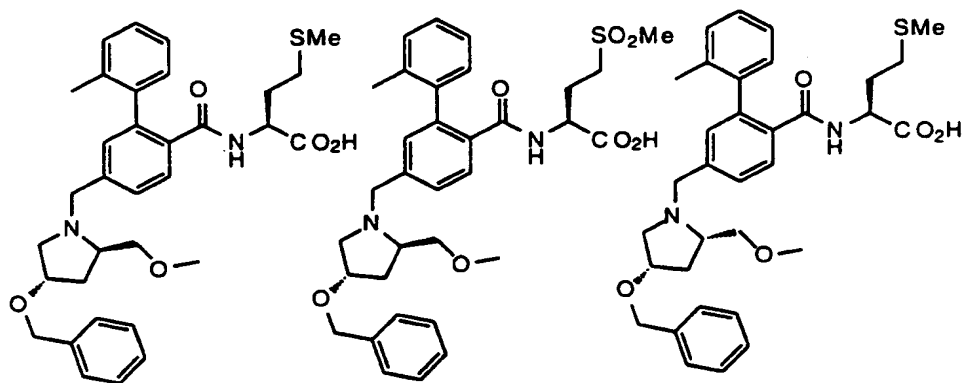


1880

235 236 237

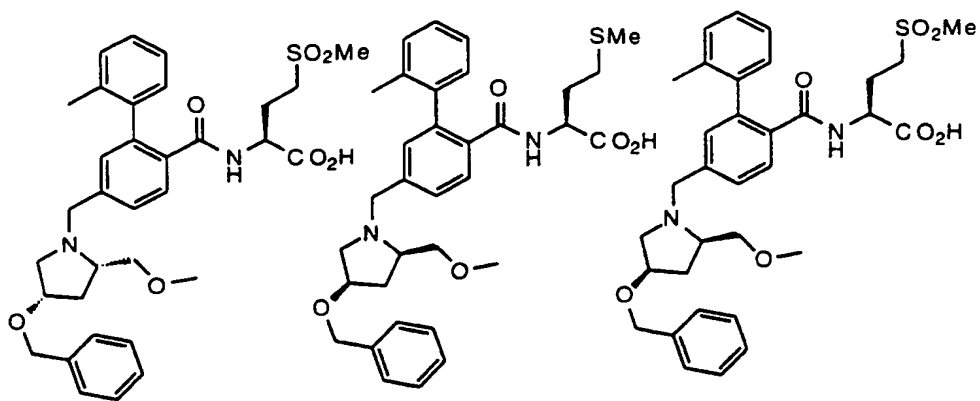


238 239 240

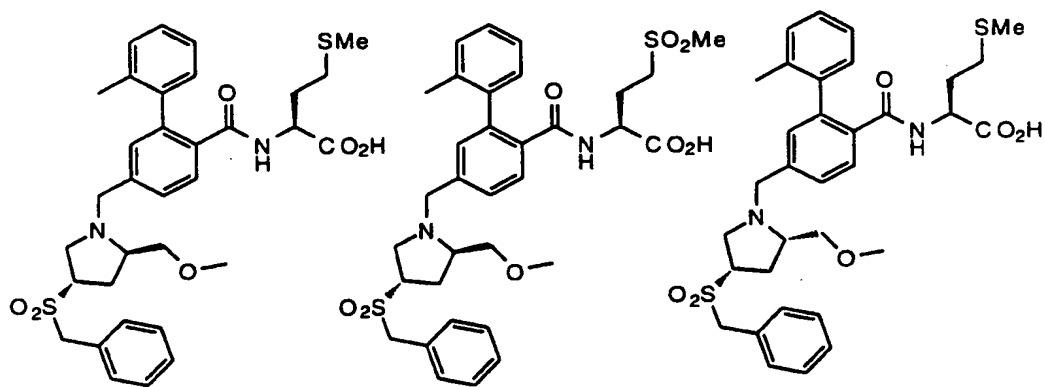
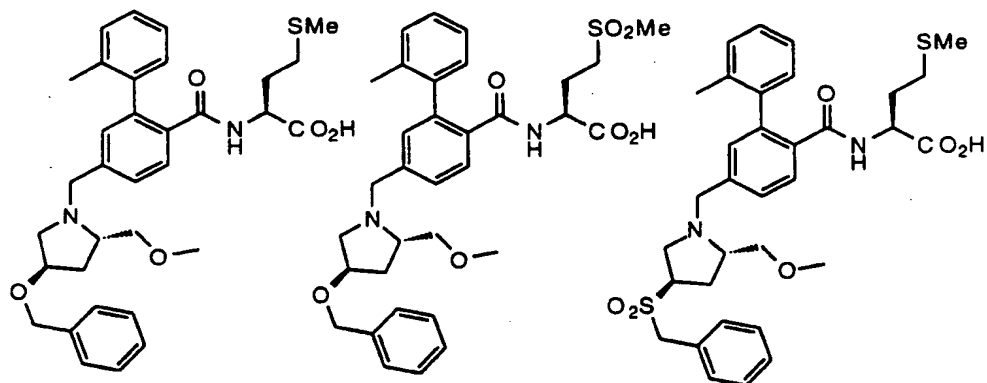


1885

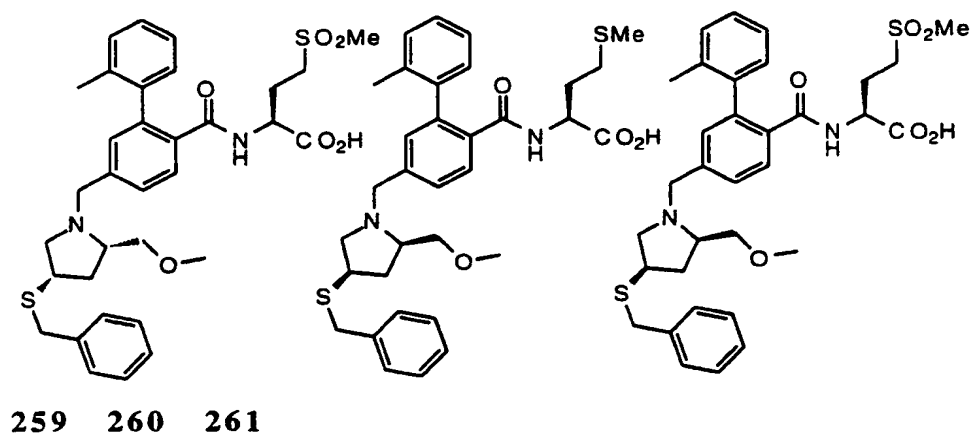
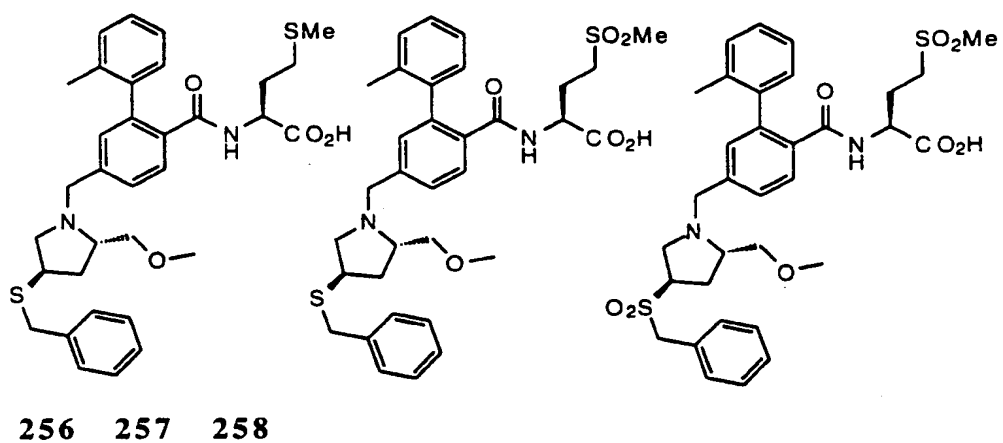
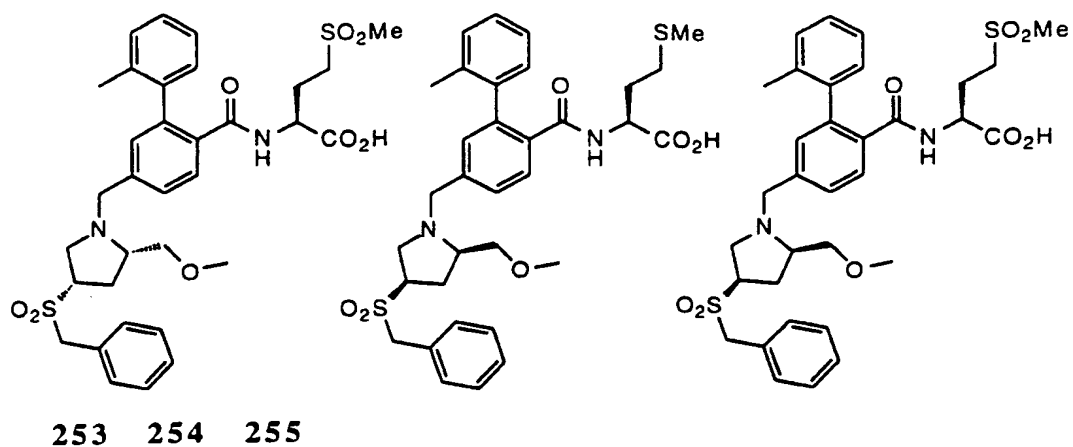
241 242 243

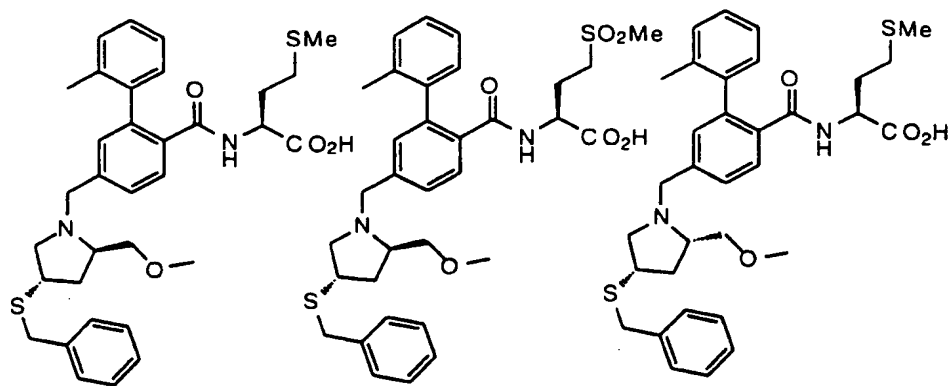


1890

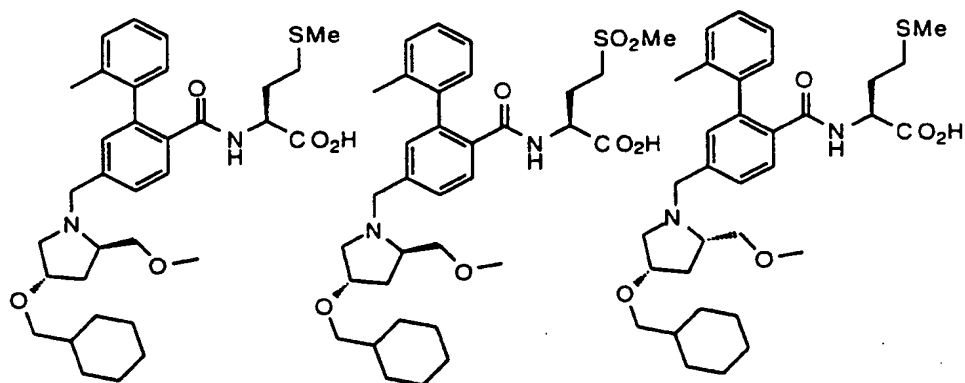


1895



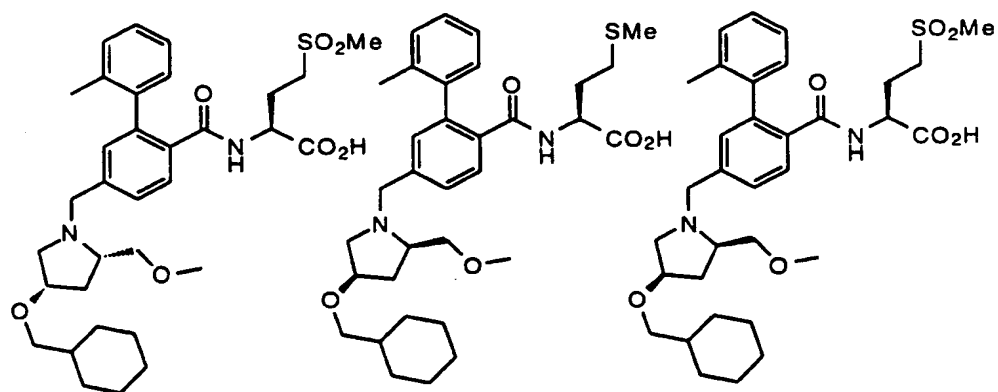


262 263 264

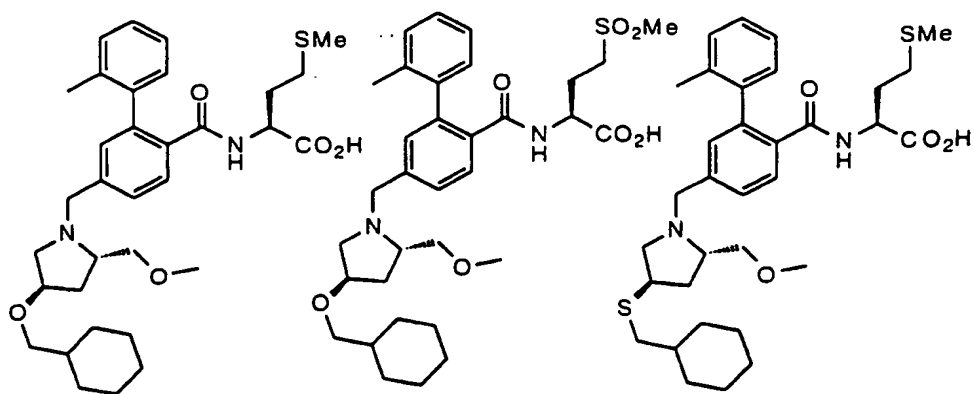


1910

265 266 267

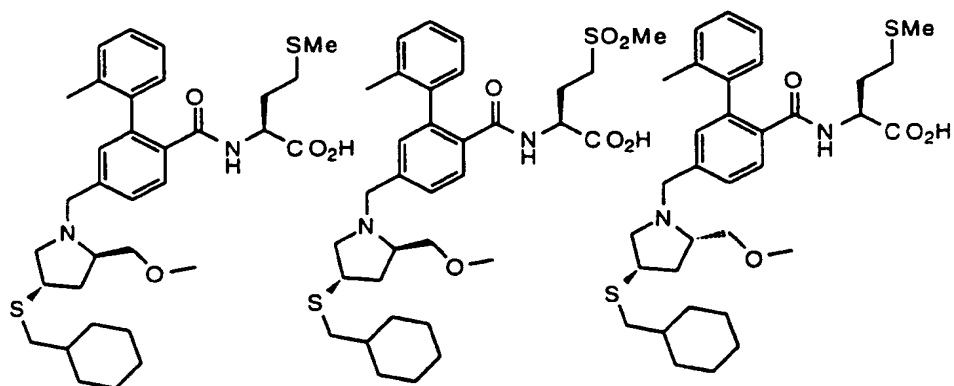


268 269 270



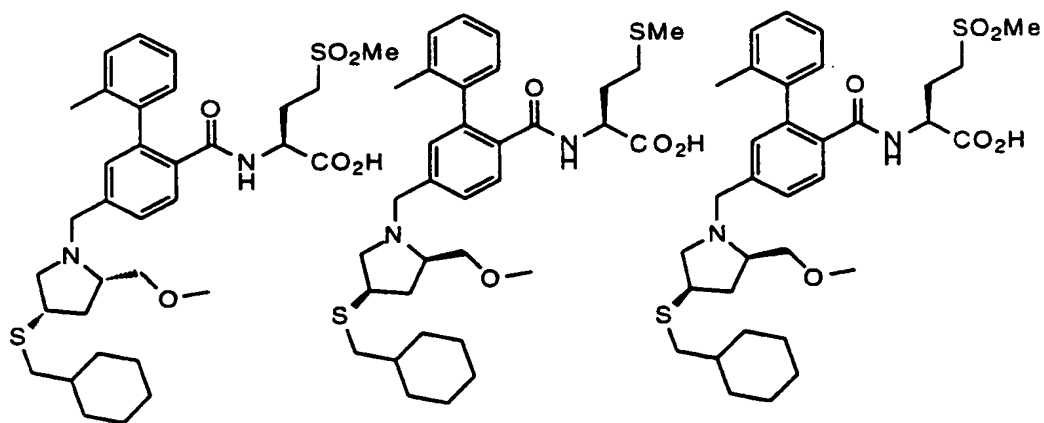
1915

271 272 273

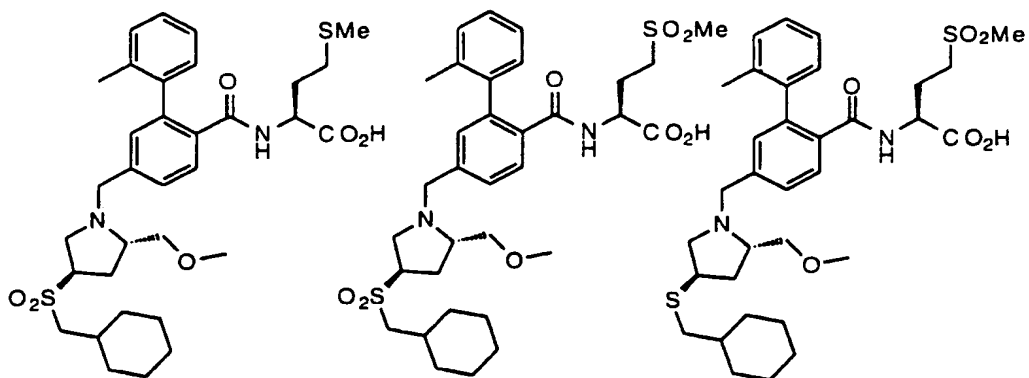


274 275 276

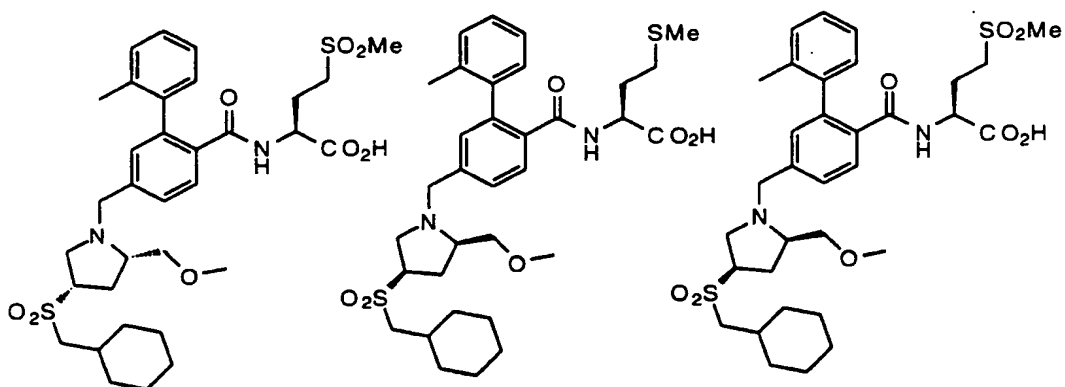
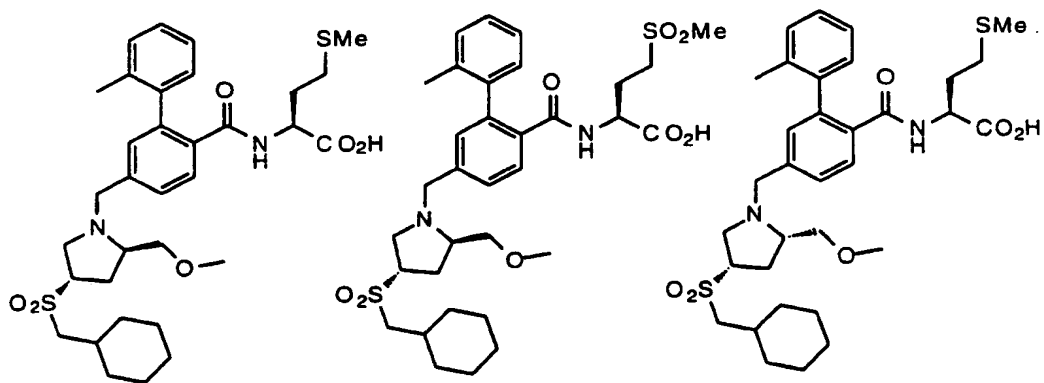
1920



277 278 279

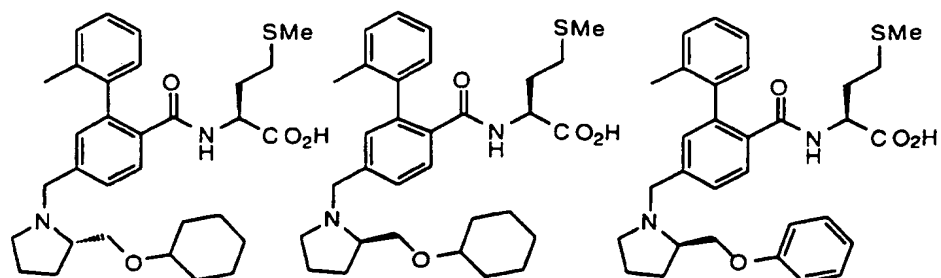


1925

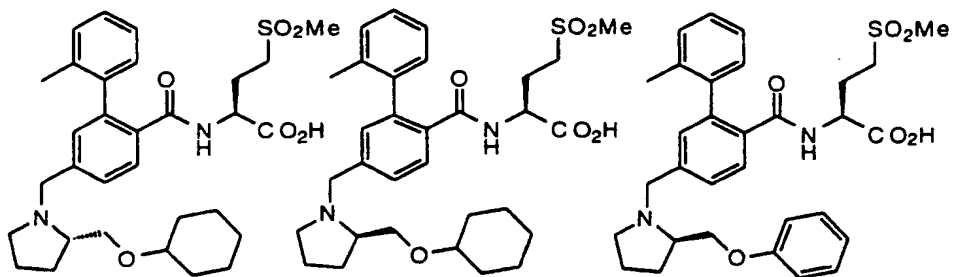
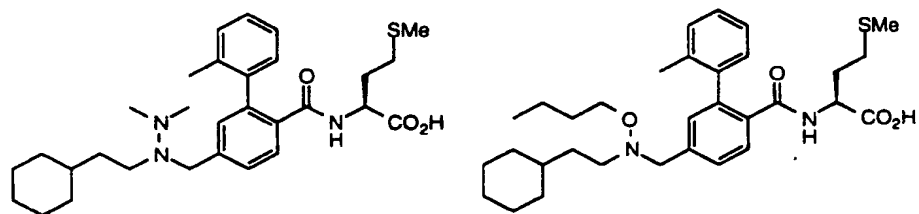
280 281 282**283 284 285**

1930

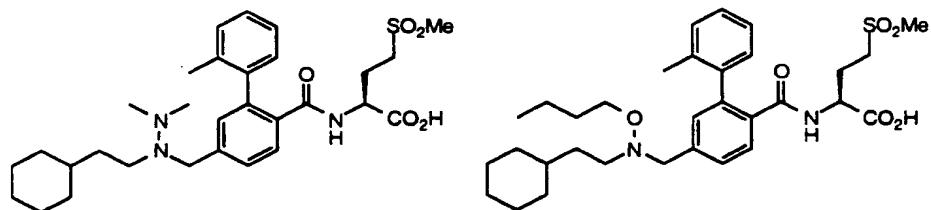
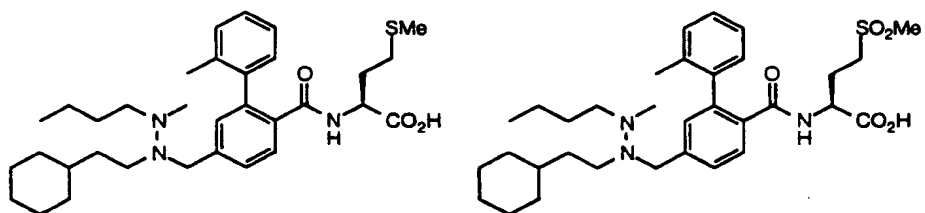
286 287 288

**289 290 291**

1935

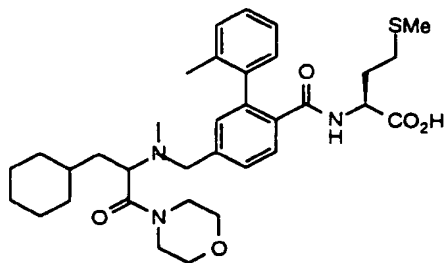
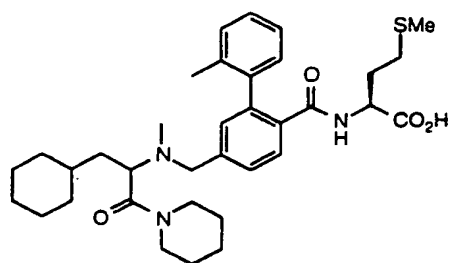
**292 293 294**

1940

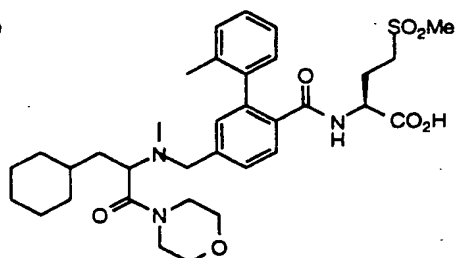
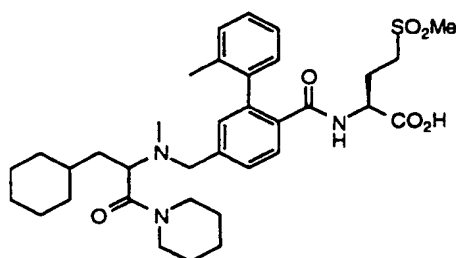
295 296**297 298**

1945

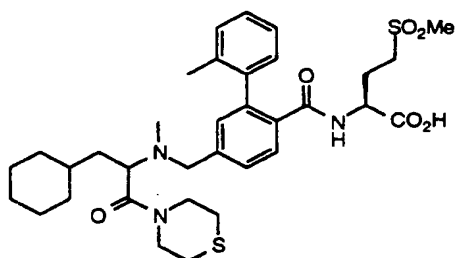
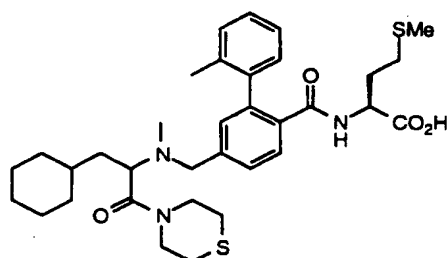
299 300



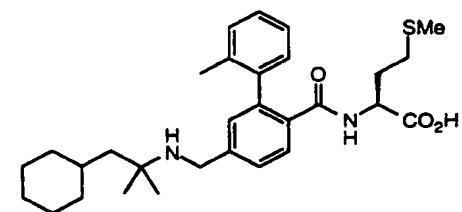
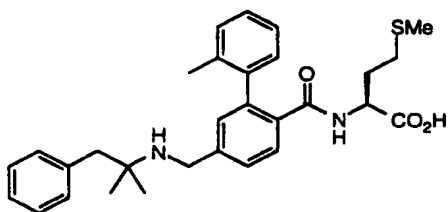
301 302



303 304



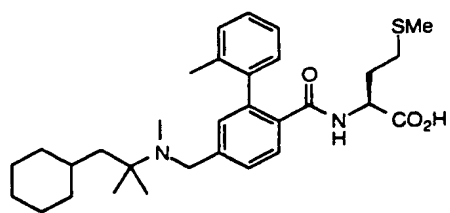
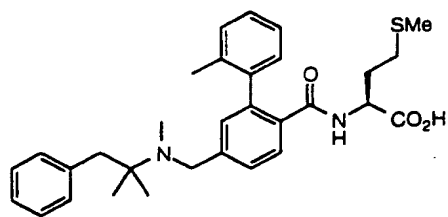
305 306



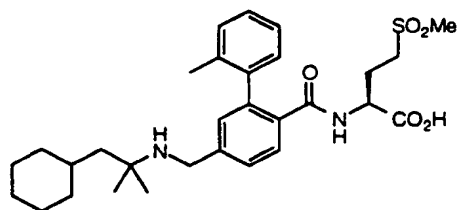
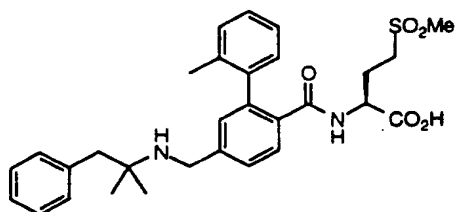
307 308

1960

309 310

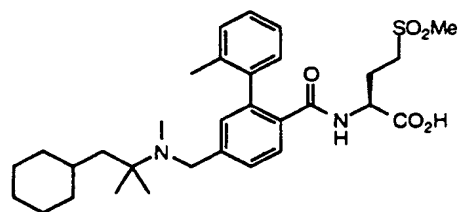
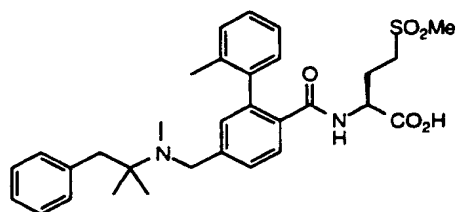


311 312



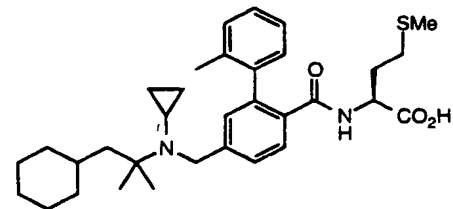
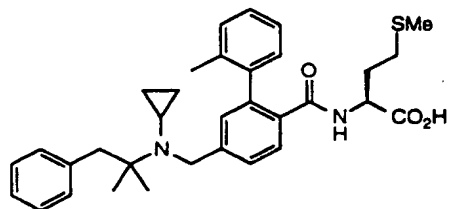
1965

313 314

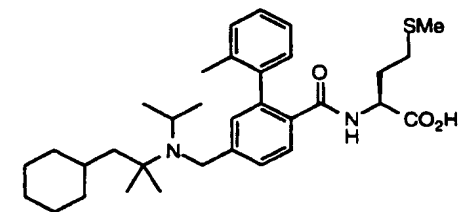
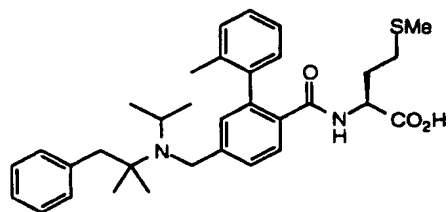


1970

315 316

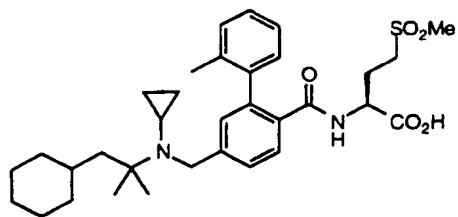
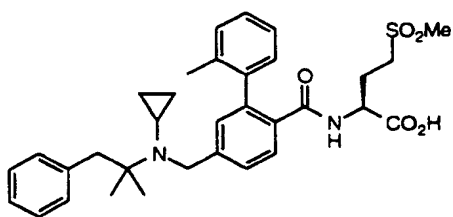


317 318

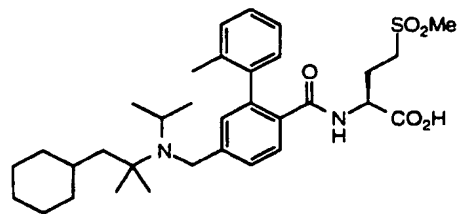
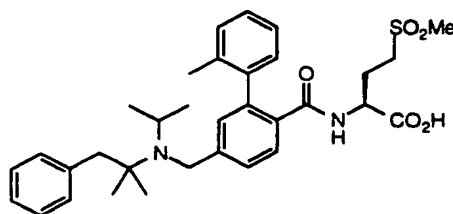


1975

319 320

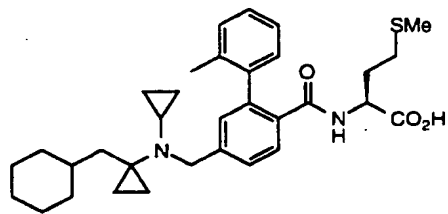
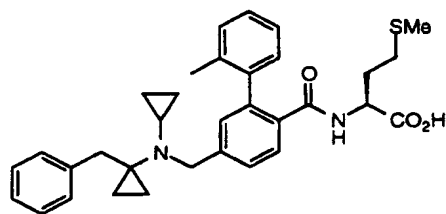


321 322



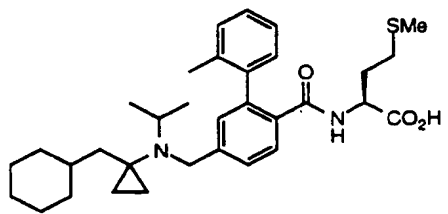
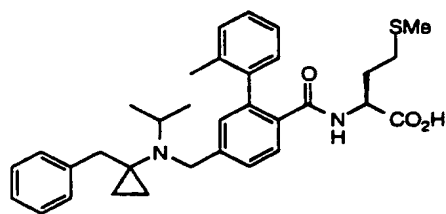
1980

323 324

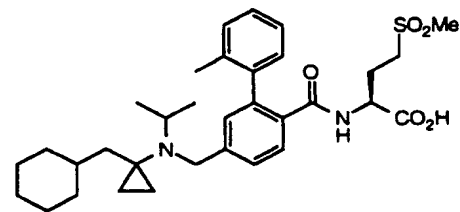
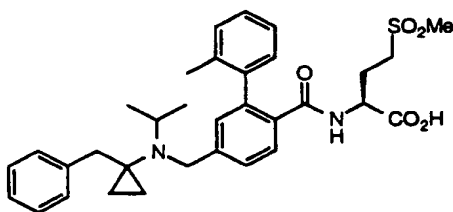


1985

325 326

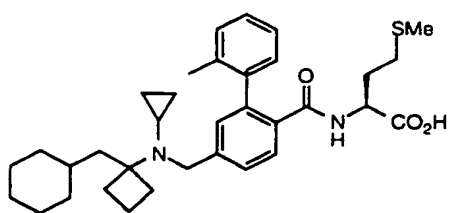
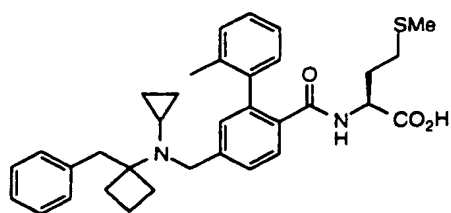


327 328

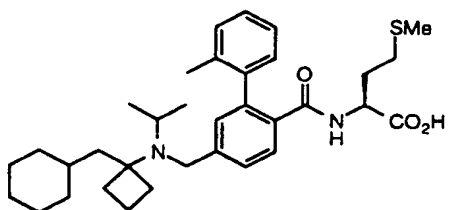
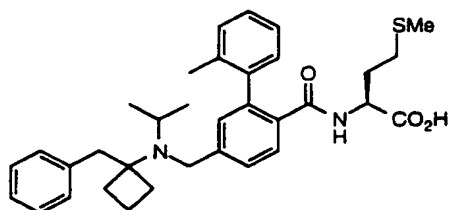


1990

329 330

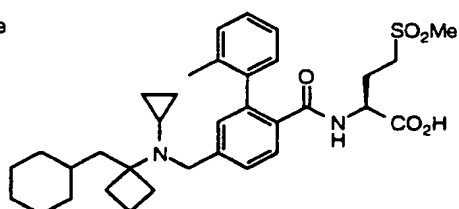
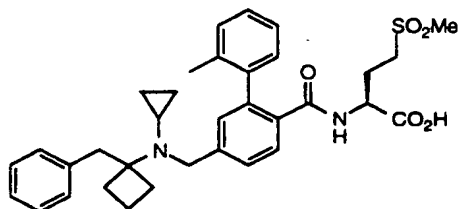


331 332



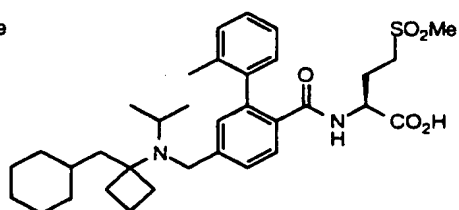
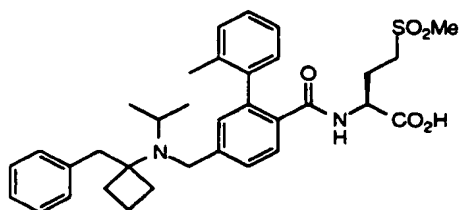
1995

333 334

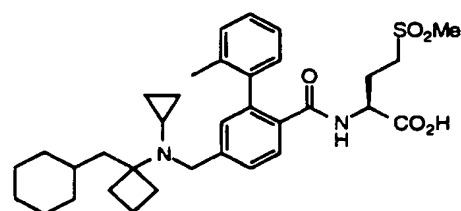
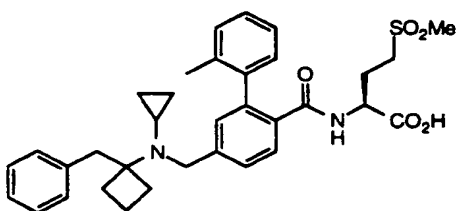


2000

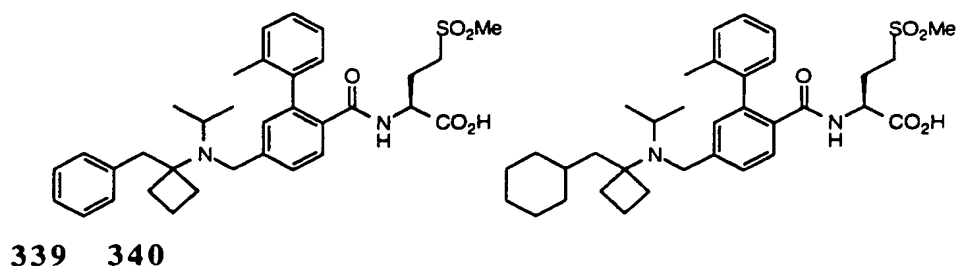
335 336



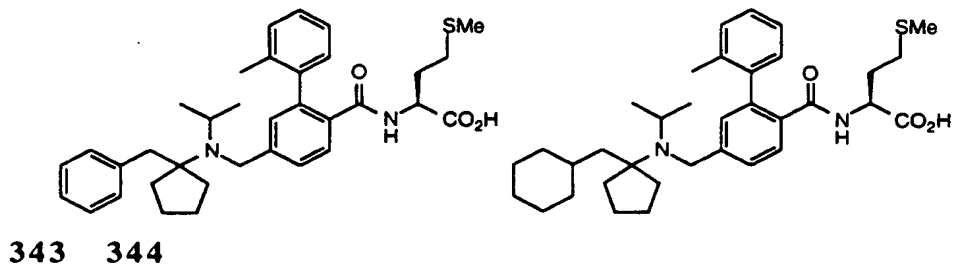
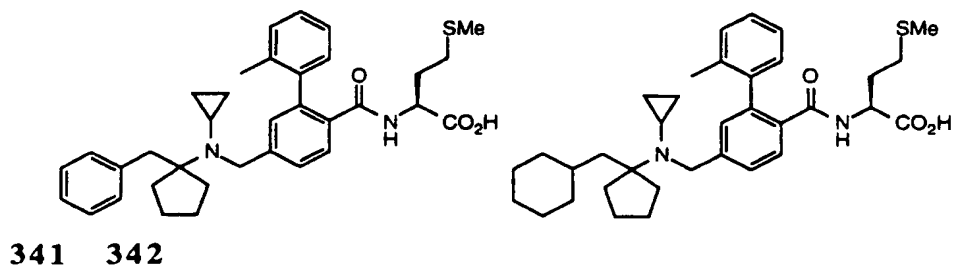
337 338



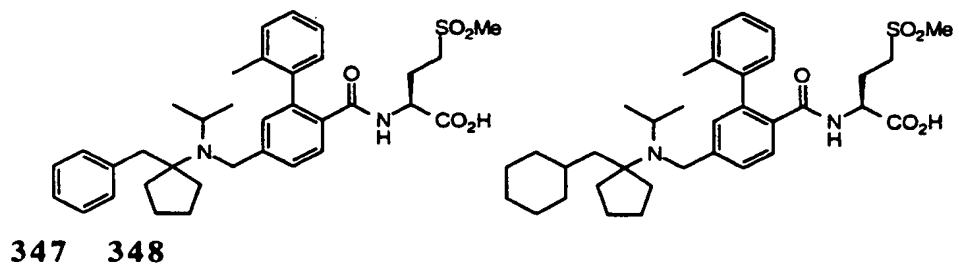
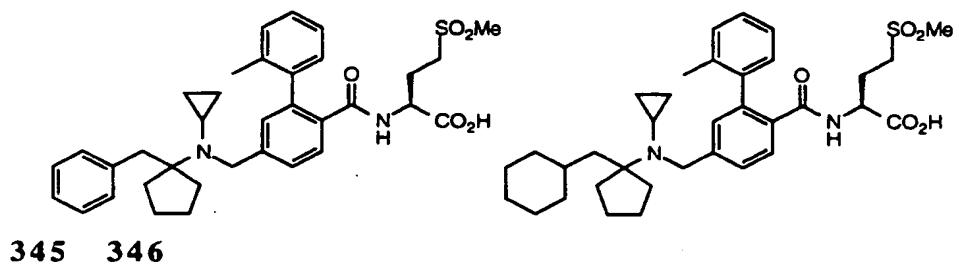
2005



2010



2015





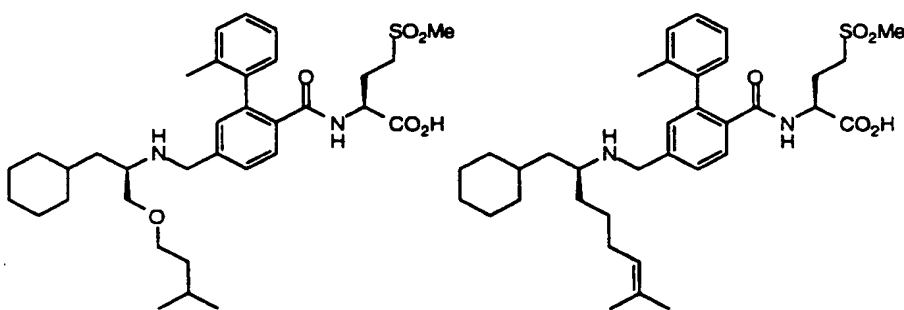
349 350



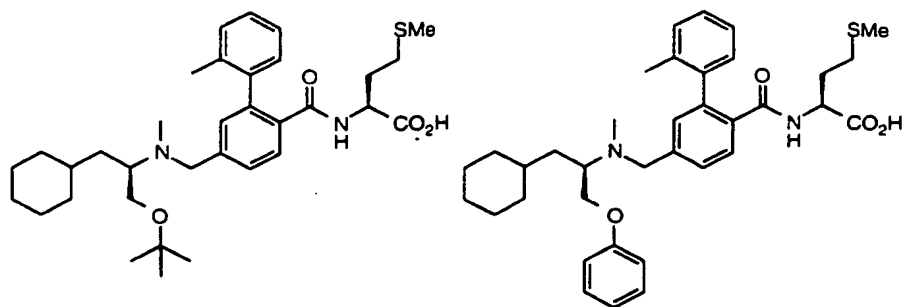
351 352



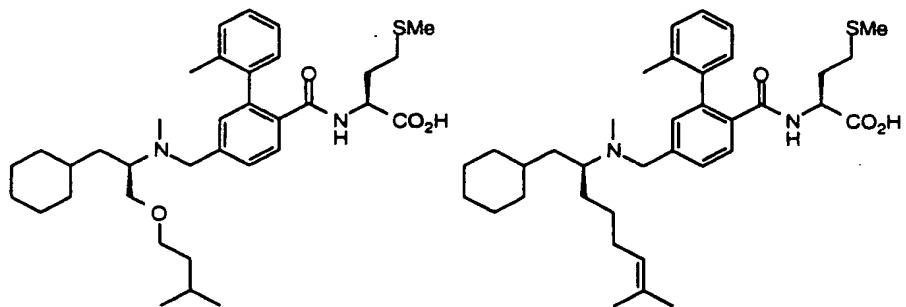
353 354



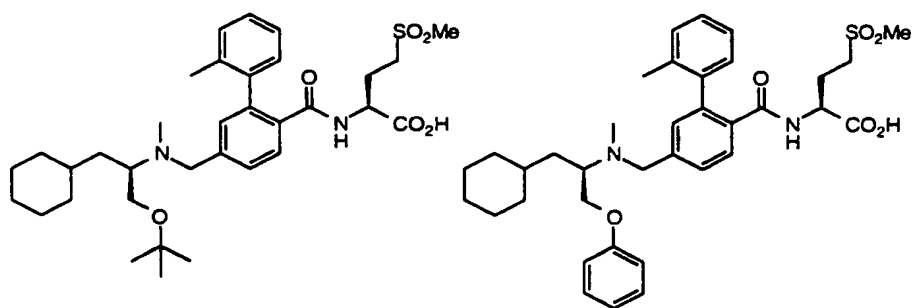
355 356



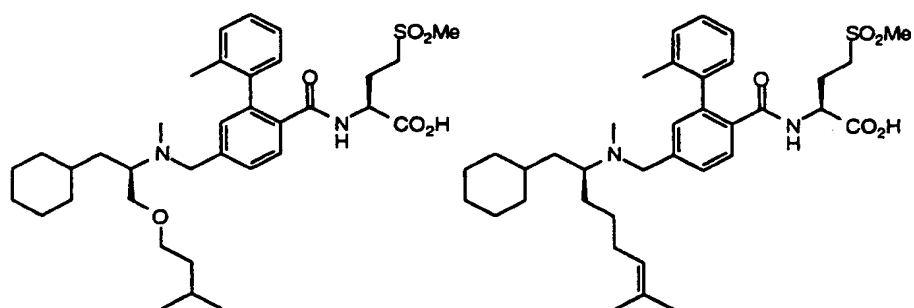
357 358



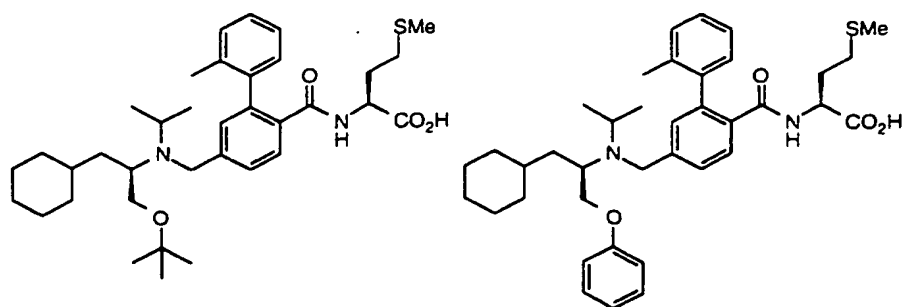
359 360



361 362

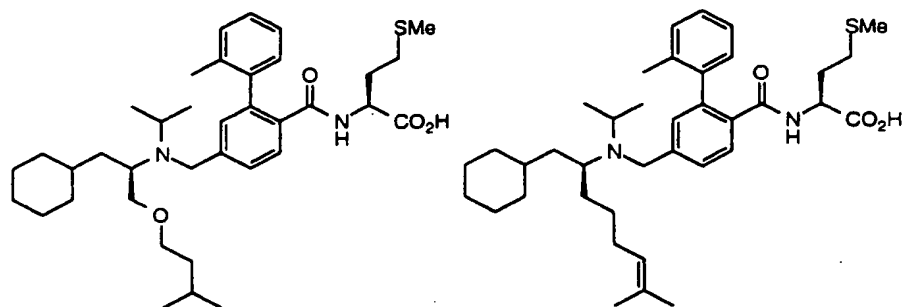


363 364

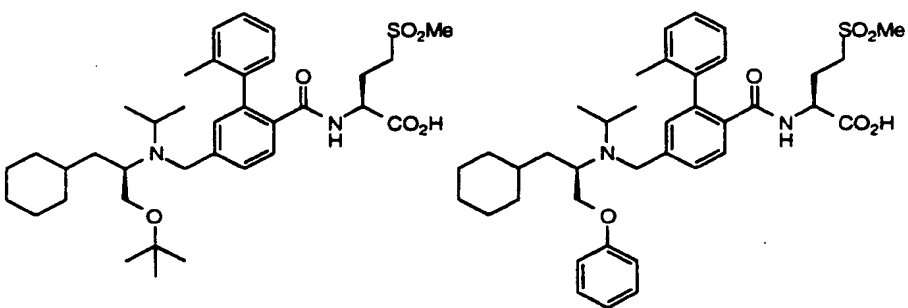


2045

365 366

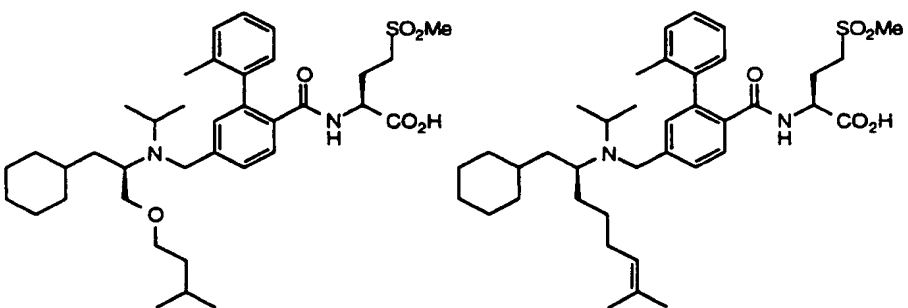


367 368



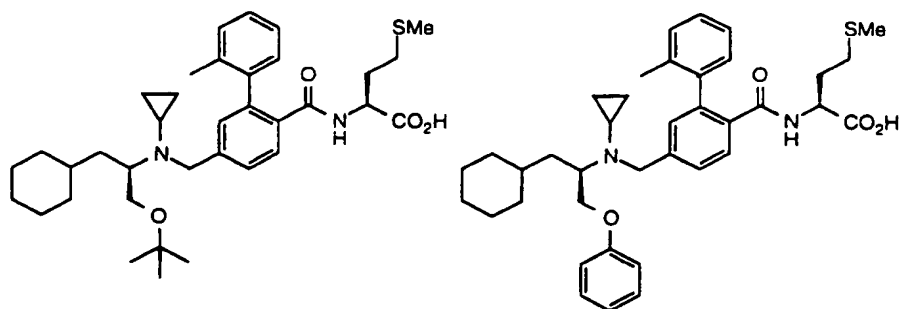
2050

369 370

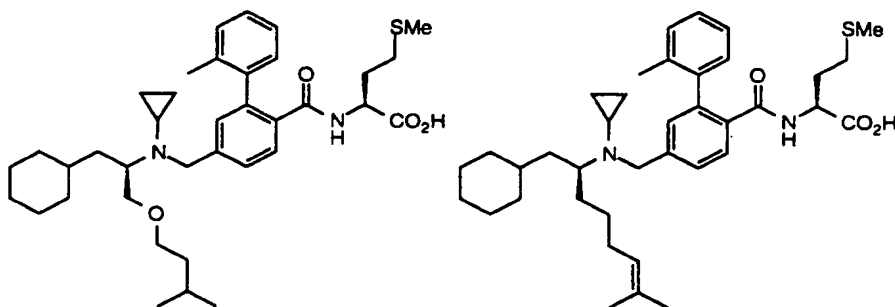


371 372

2055

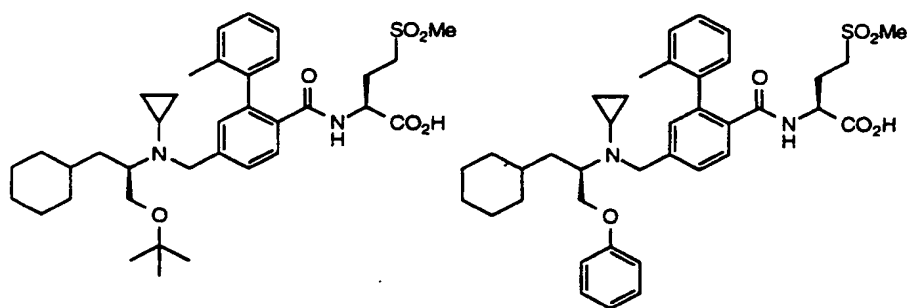


373 374

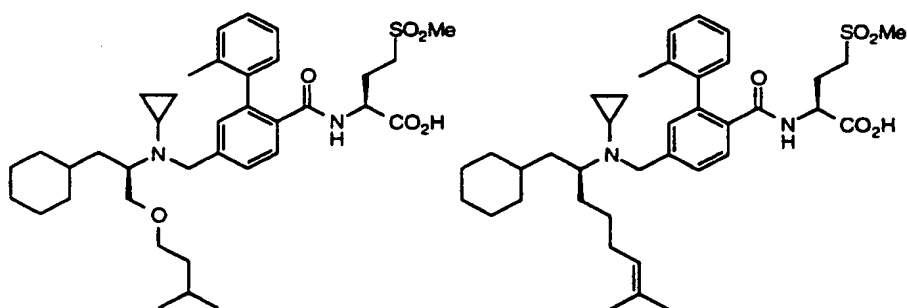


2060

375 376



377 378

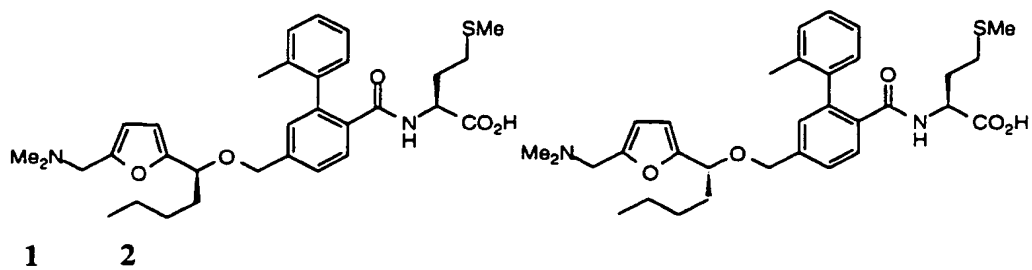


2065

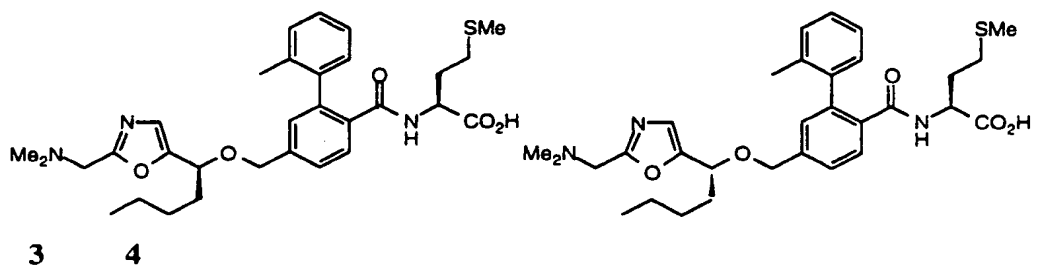
379 380

Table 7. Ethers of the Type A-OL₁

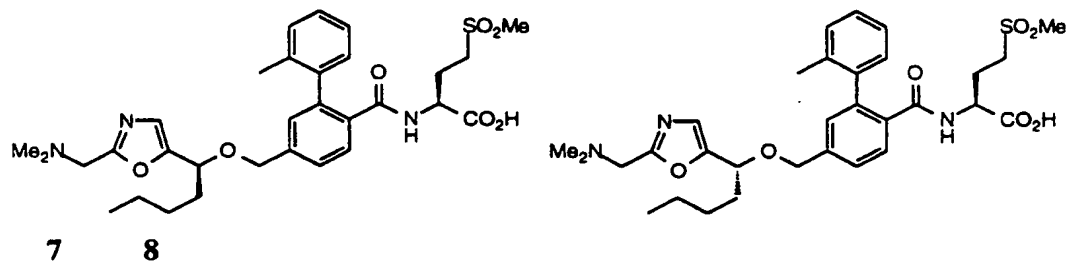
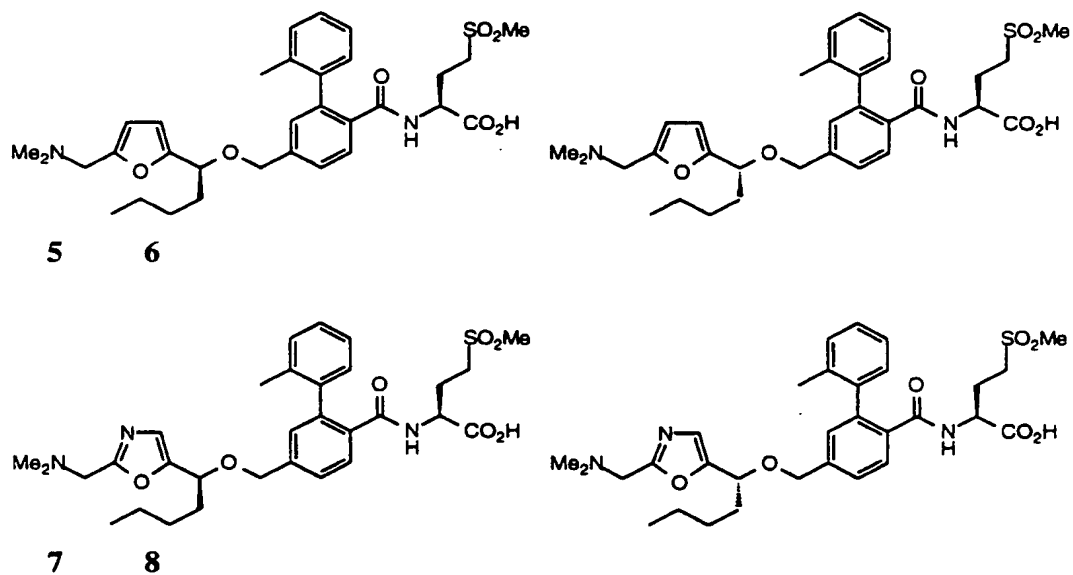
2070

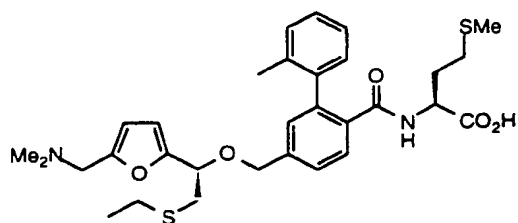


2075

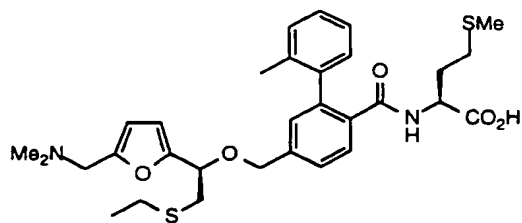


2080



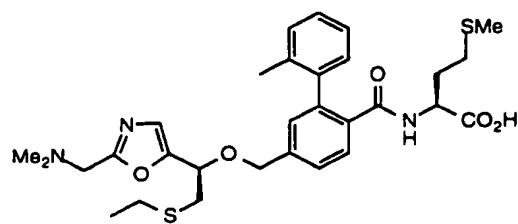


9

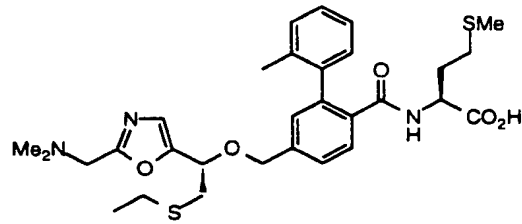


10

2085

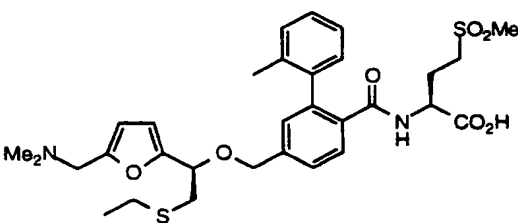


11

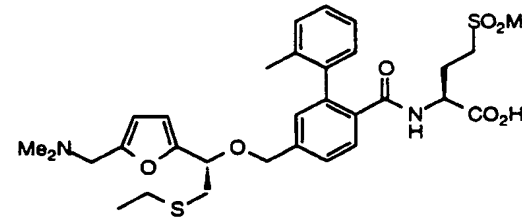


12

2090

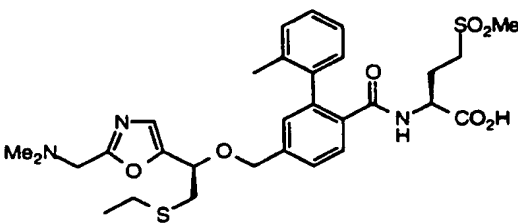


13

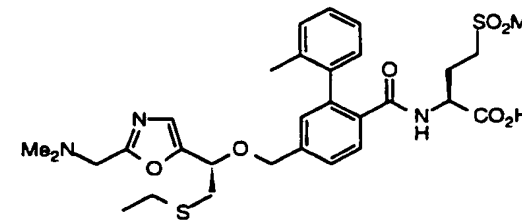


14

2095

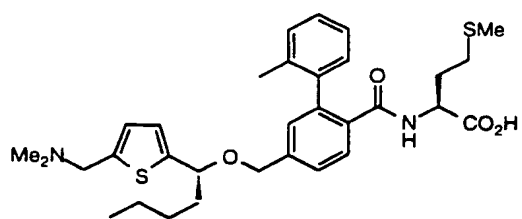
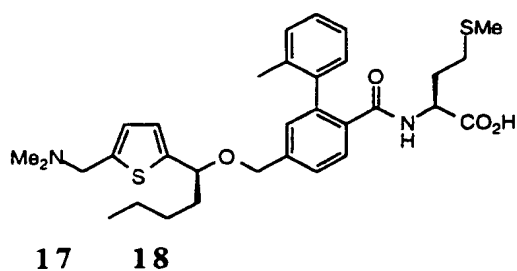


15

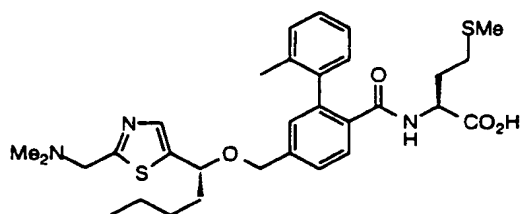
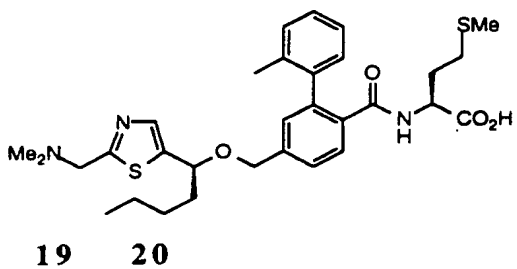


16

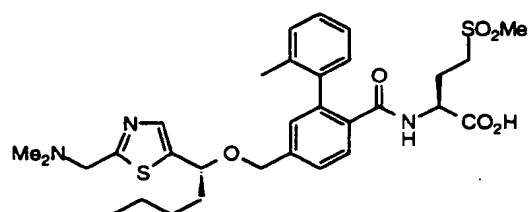
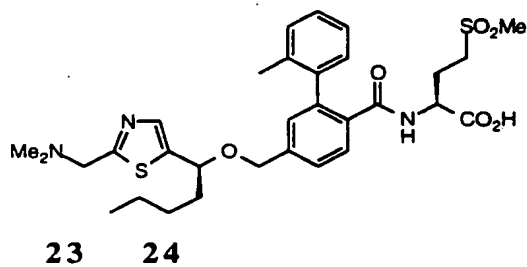
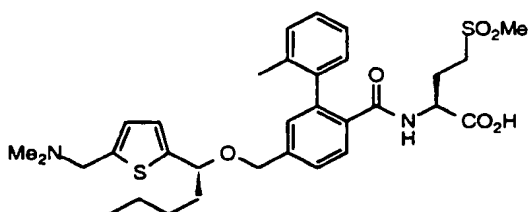
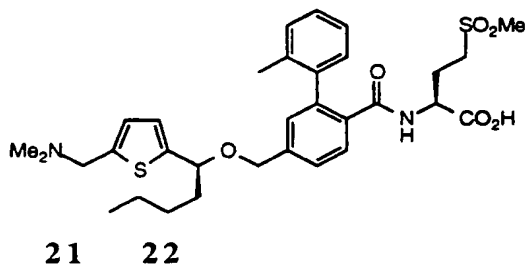
2100



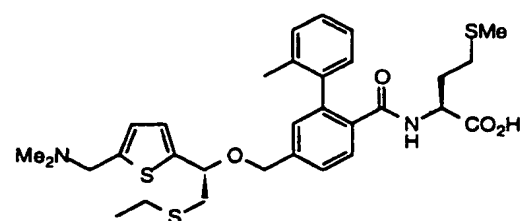
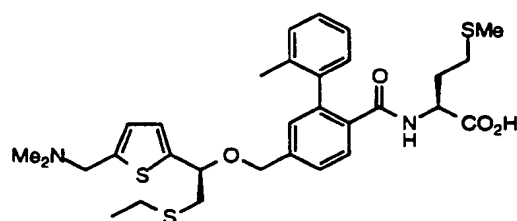
2105



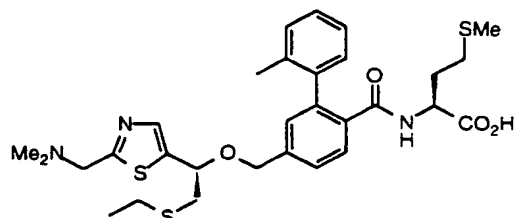
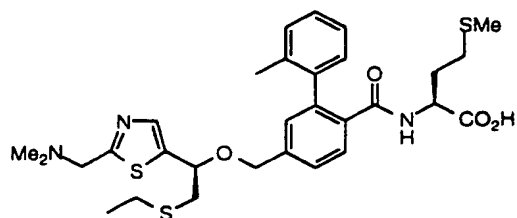
2110



2115

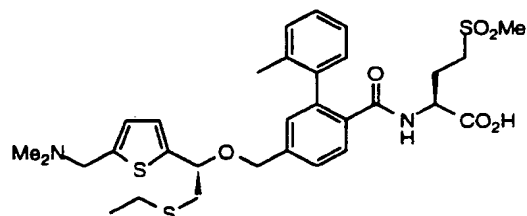
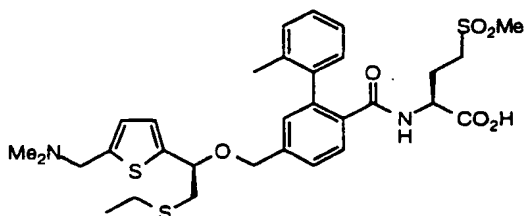


25 26



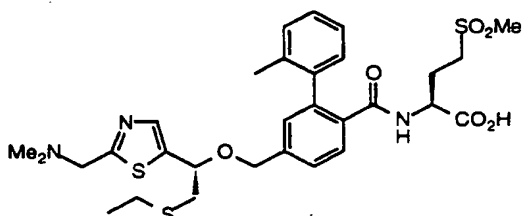
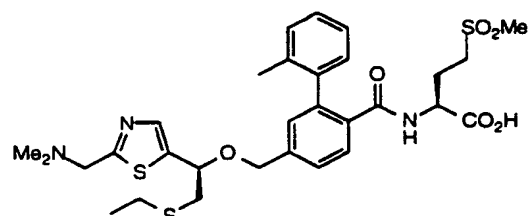
2120

27 28



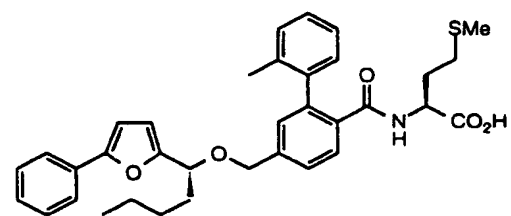
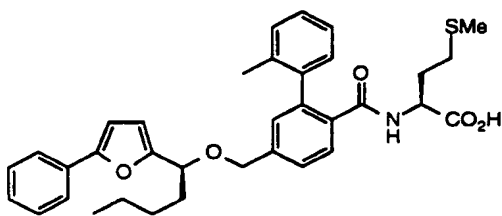
2125

29 30



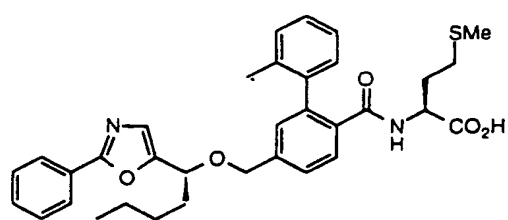
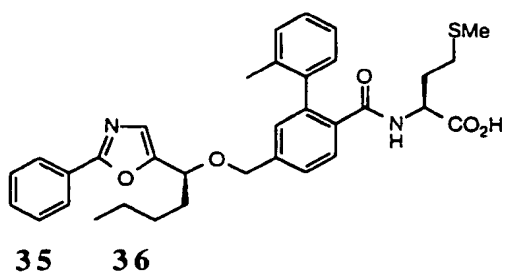
31 32

2130

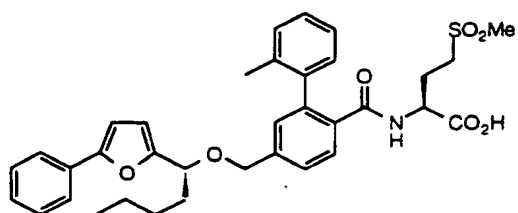
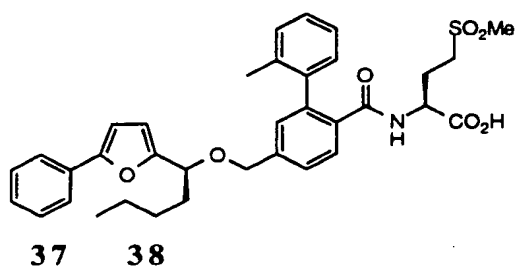


33 34

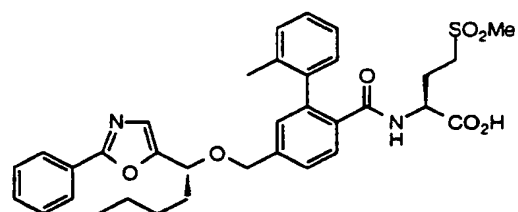
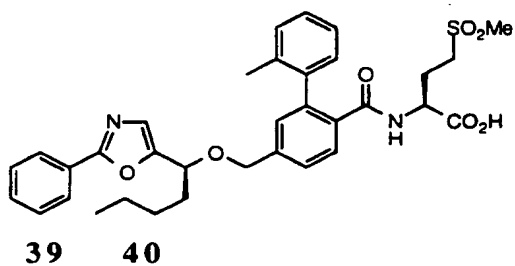
2135



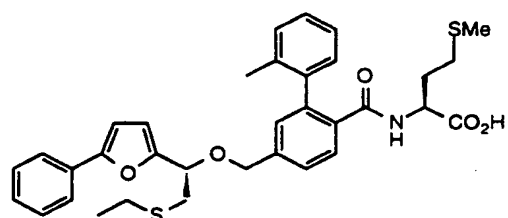
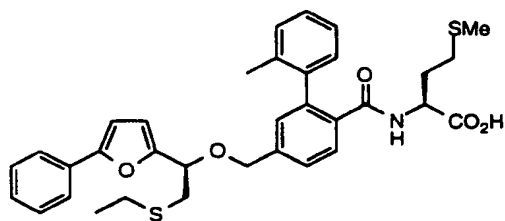
2140



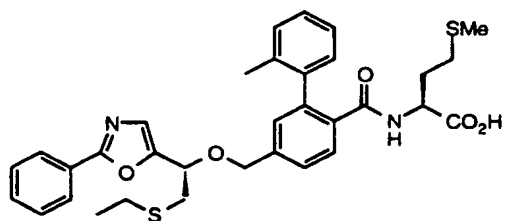
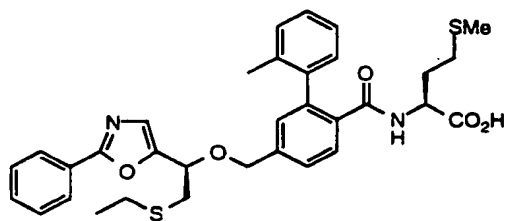
2145



41 **42**

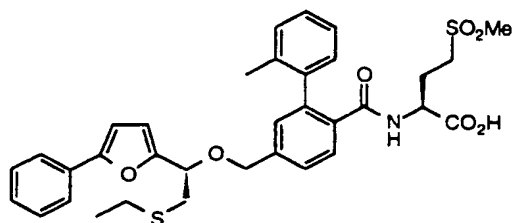
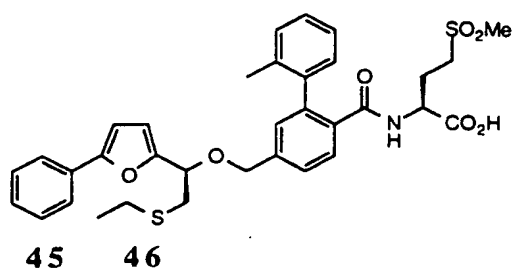


2150

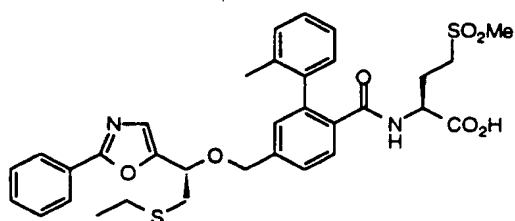
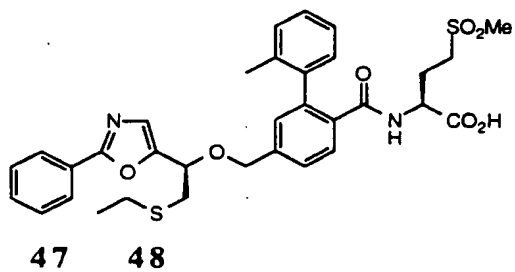


43 44

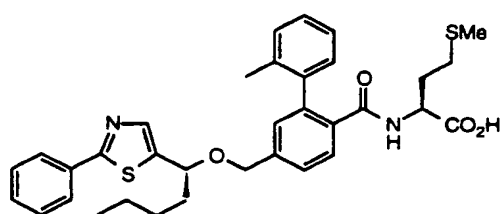
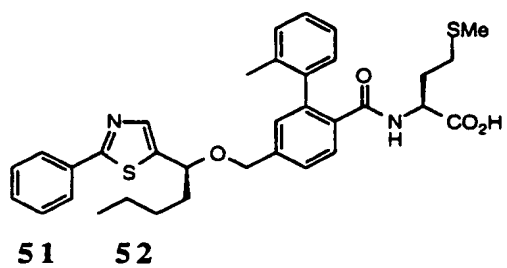
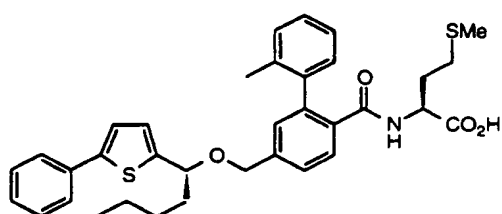
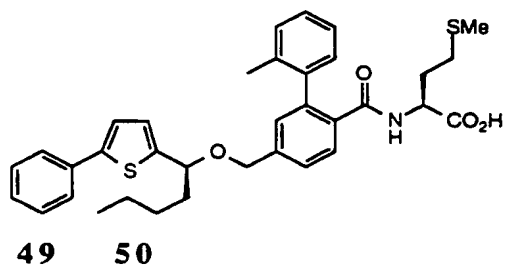
2155



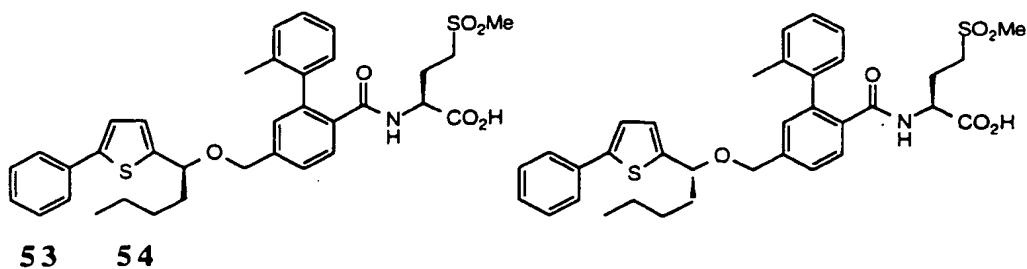
2160



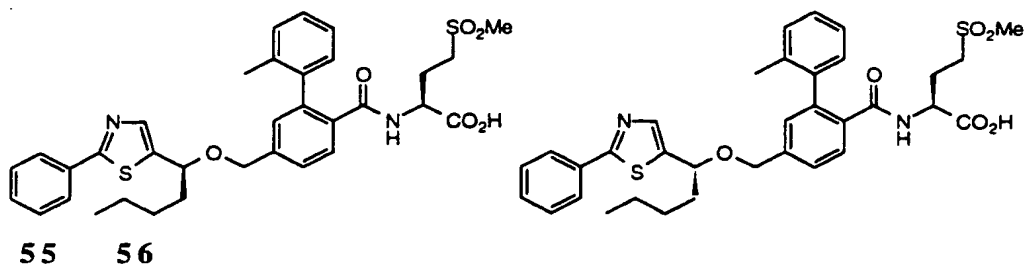
2165



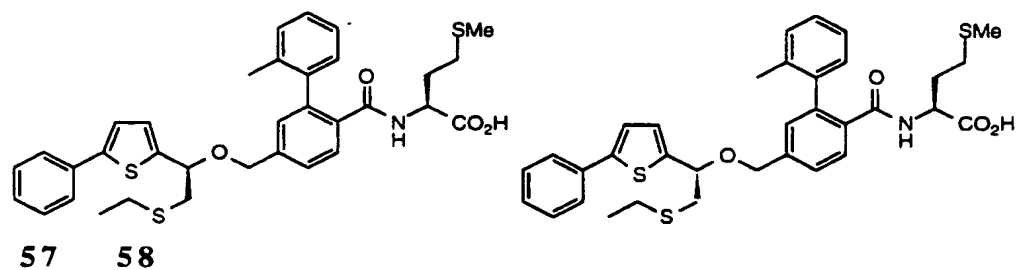
2170



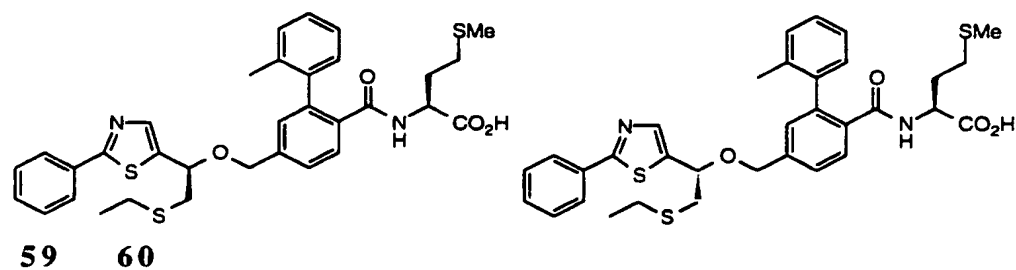
2175

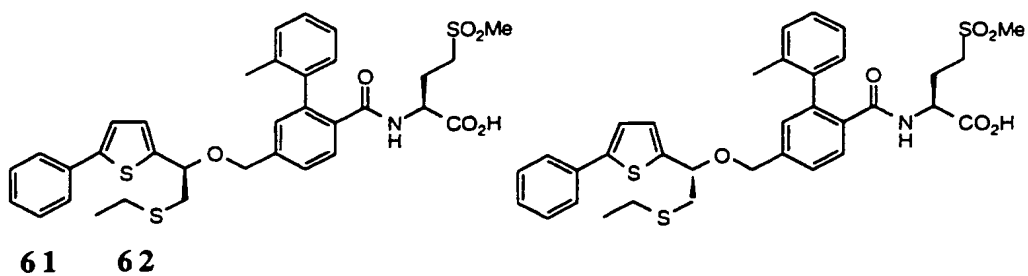


2180

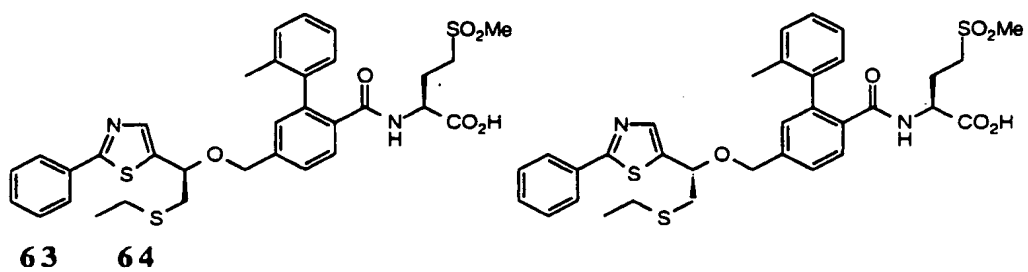


2185

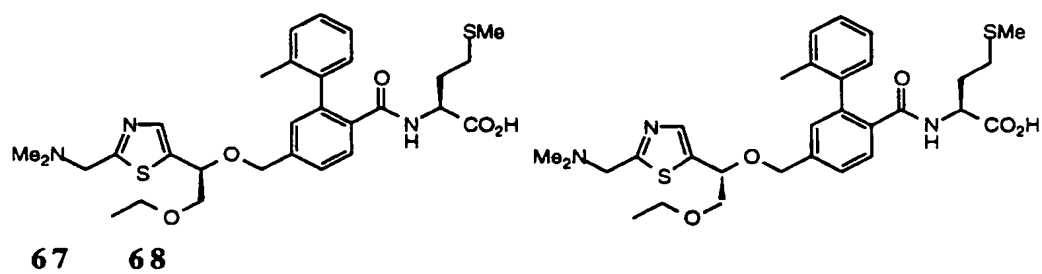
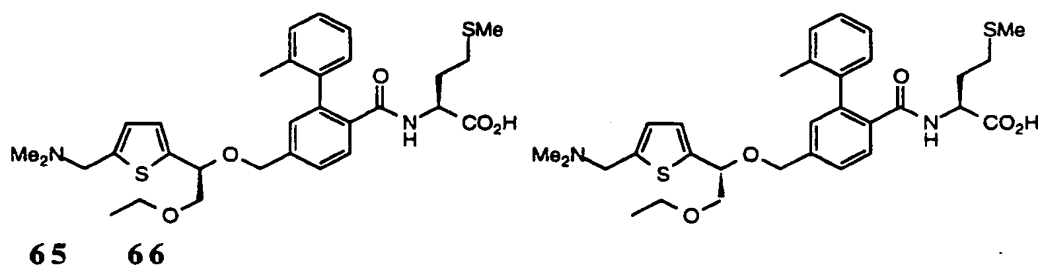




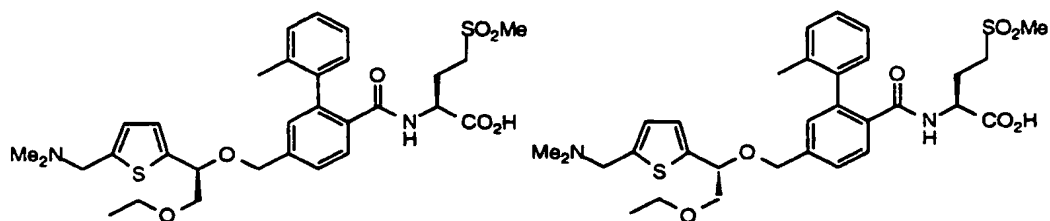
2190



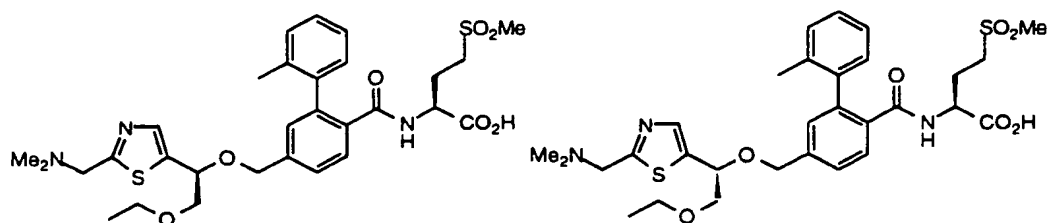
2195



2200

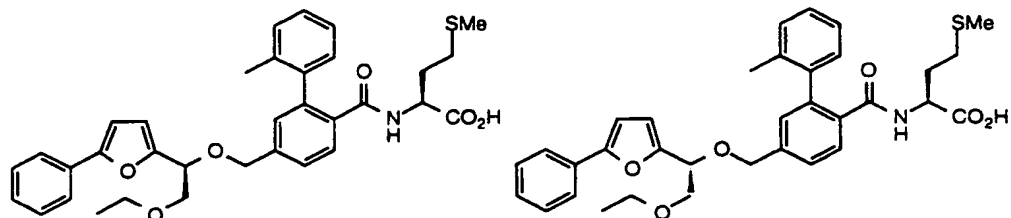


69 70

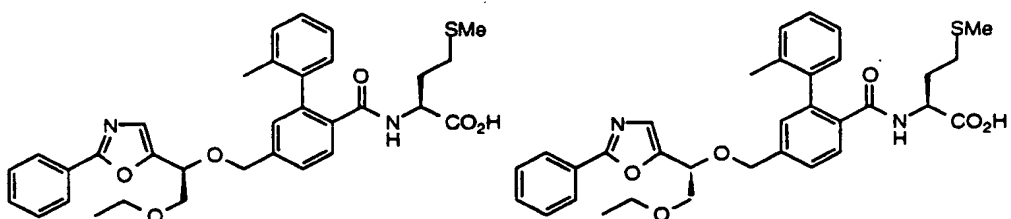


71 72

2205

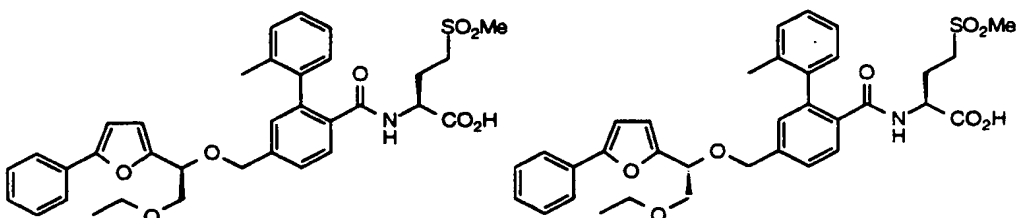


73 74



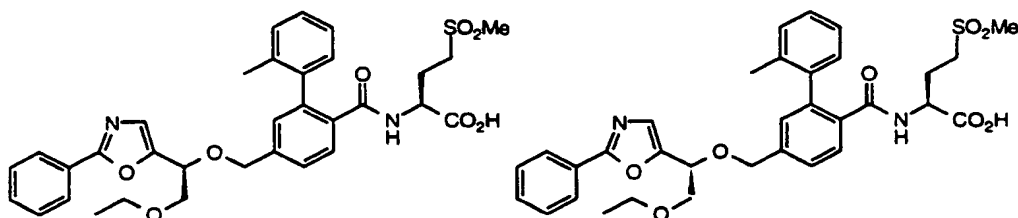
75 76

2210



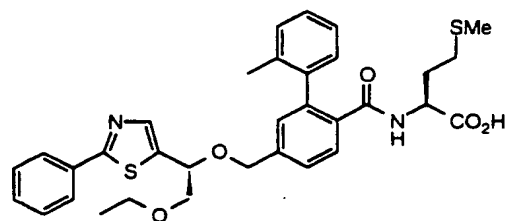
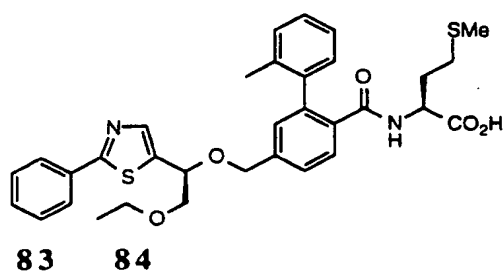
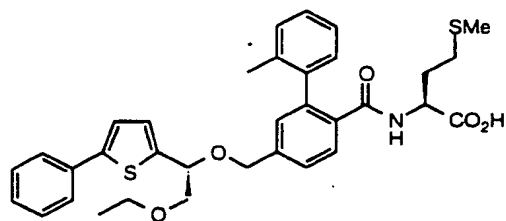
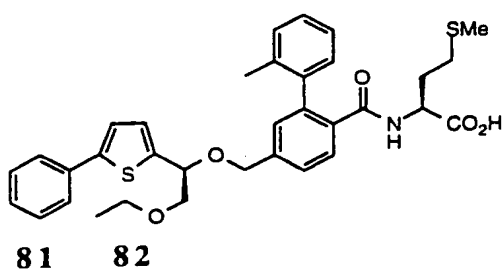
77 78

2215

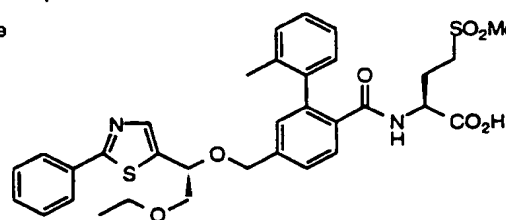
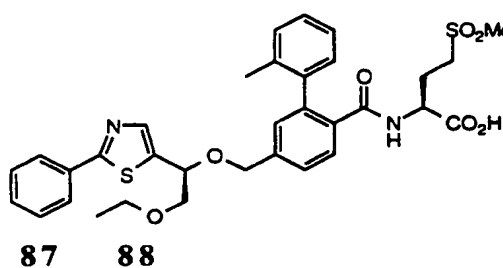
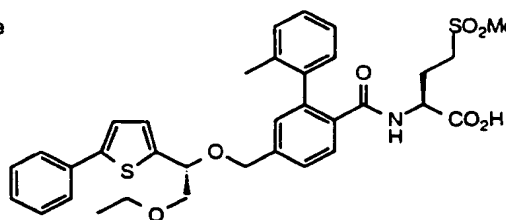
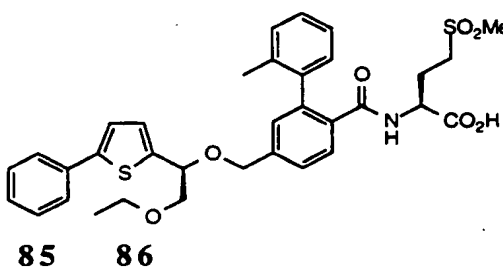


79 80

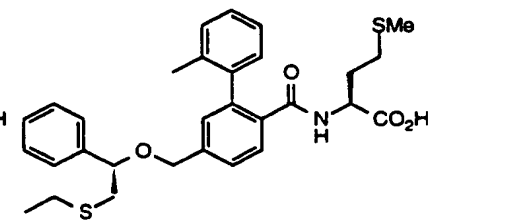
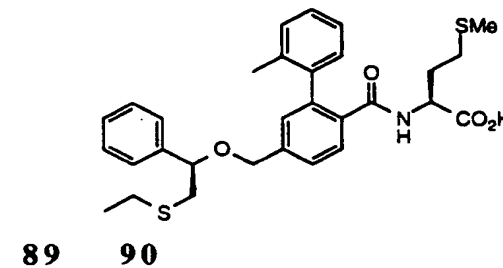
2220



2225

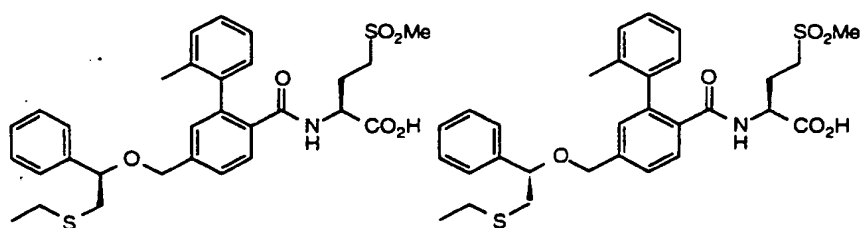


2230

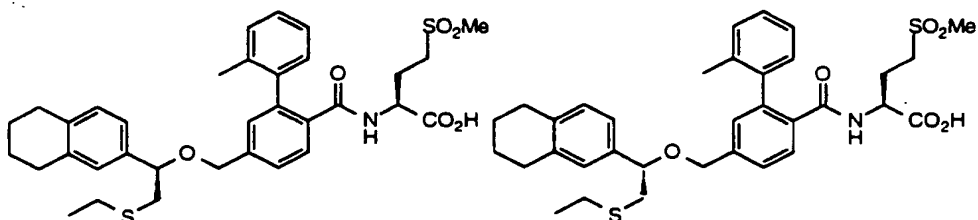


2235

91 92

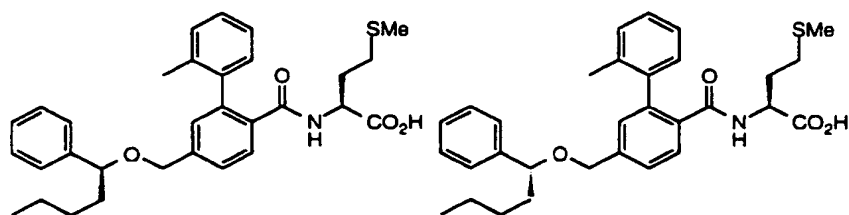


93 94

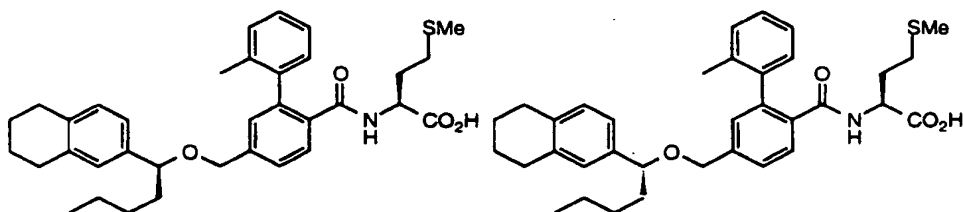


2240

95 96

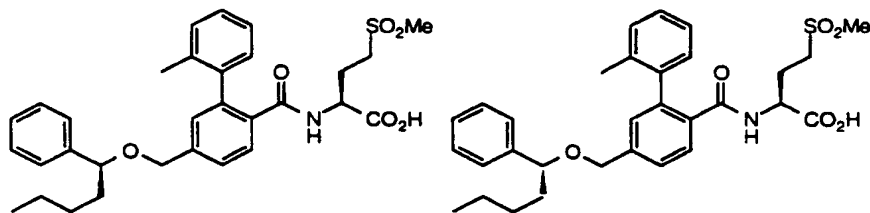


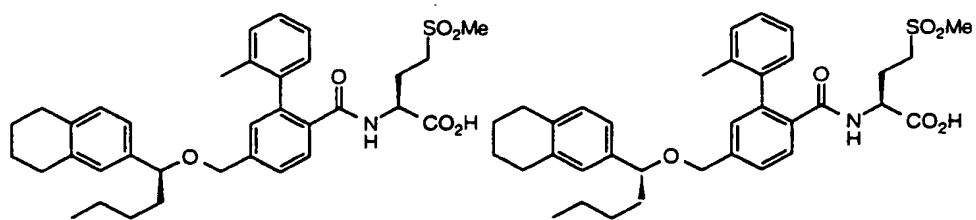
97 98



2245

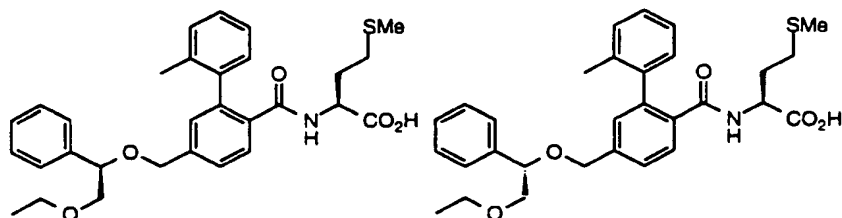
99 100



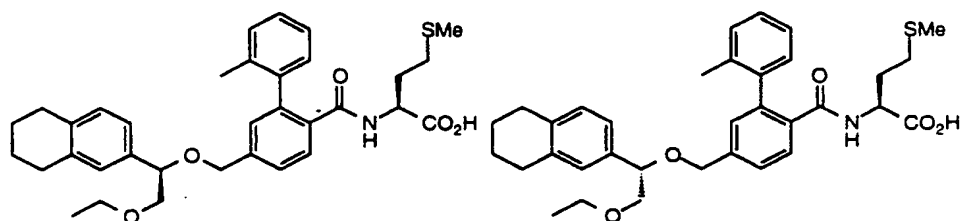


2250

101 102

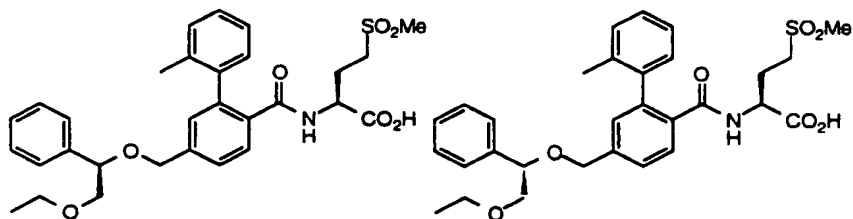


103 104



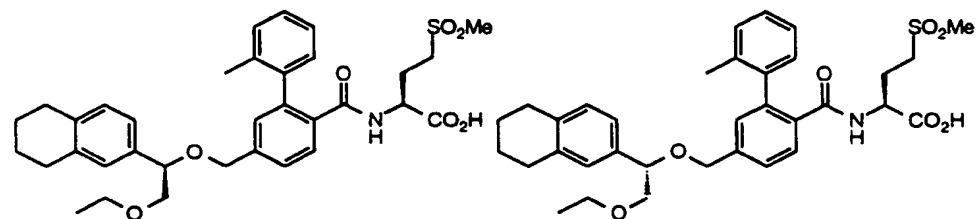
2255

105 106



107 108

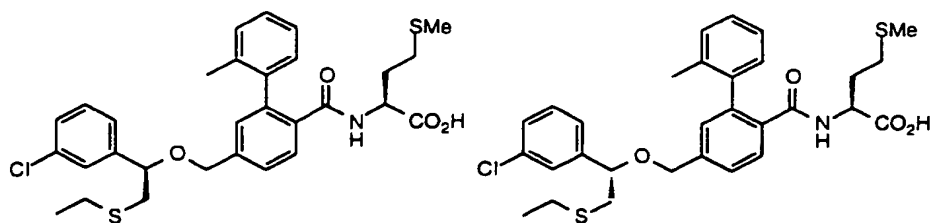
2260



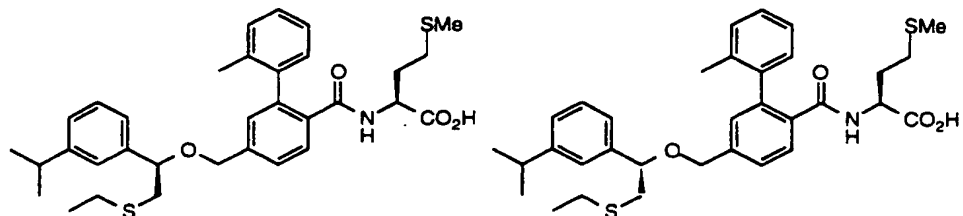
109 110

2265

111 112

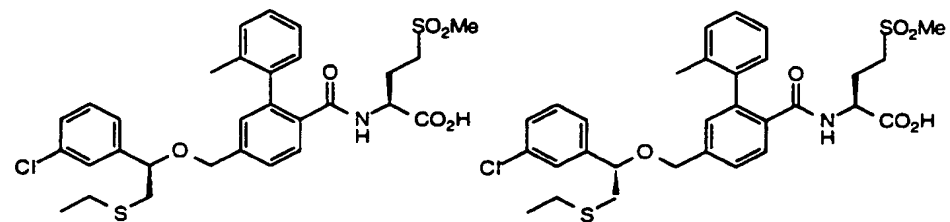


113 114

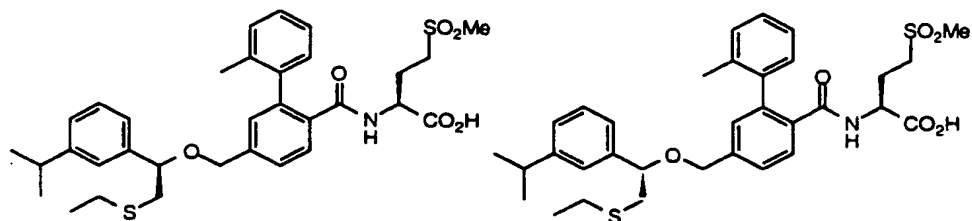


2270

115 116

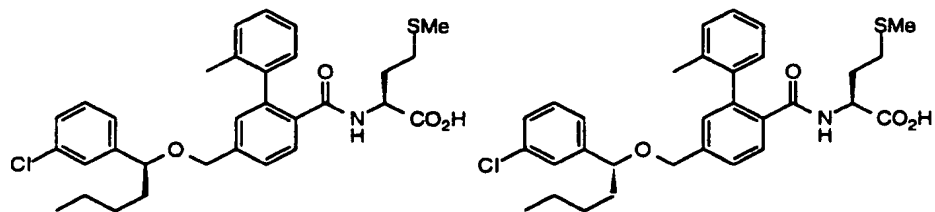


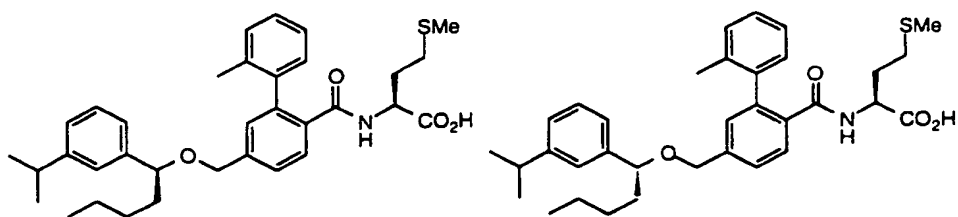
117 118



2275

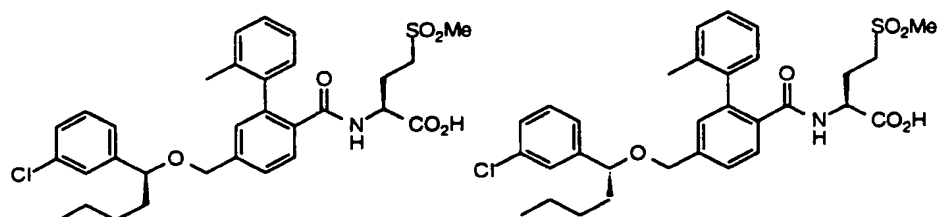
119 120



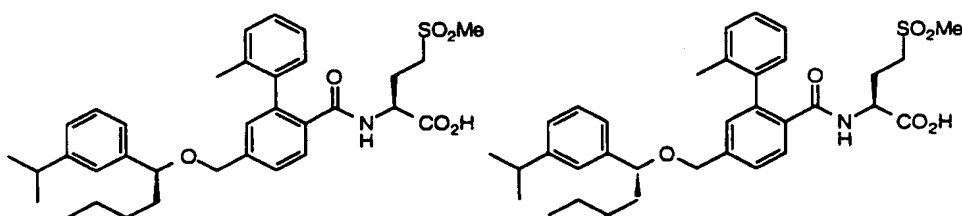


2280

121 122

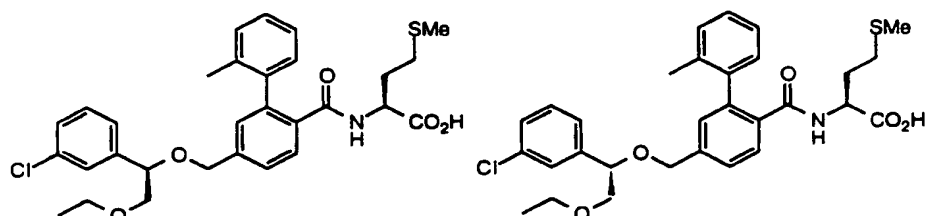


123 124



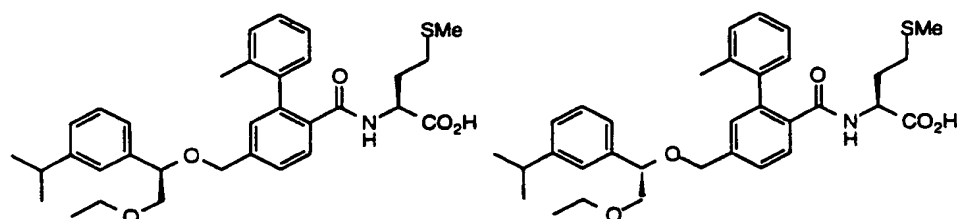
2285

125 126

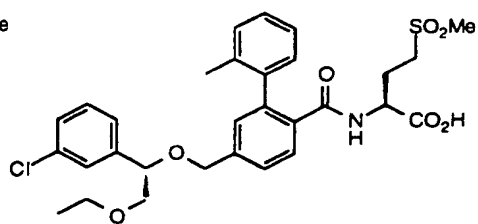
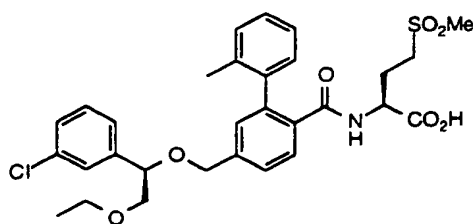


127 128

2290

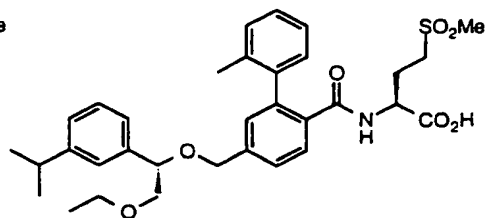
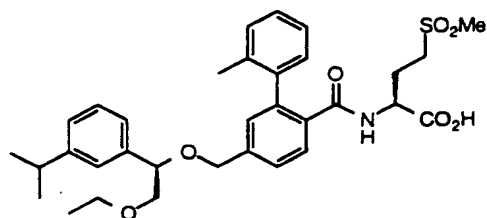


129 130

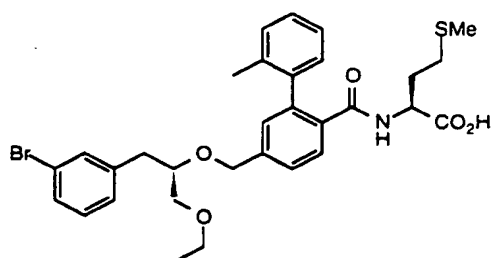
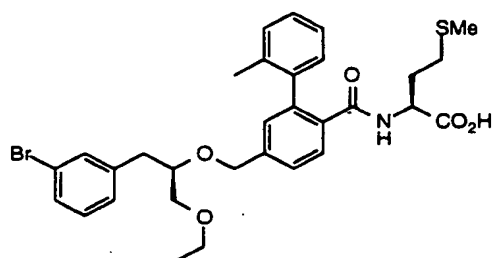


2295

131 132

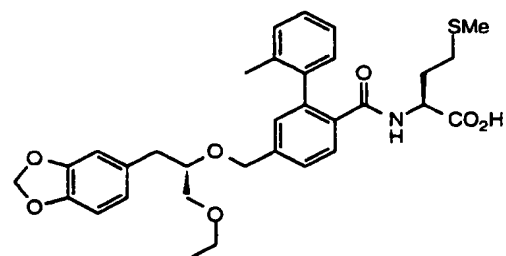
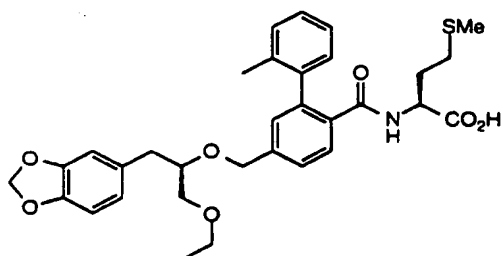


133 134



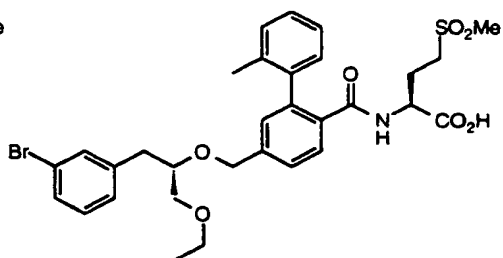
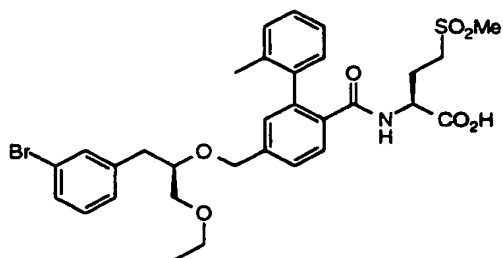
2300

135 136

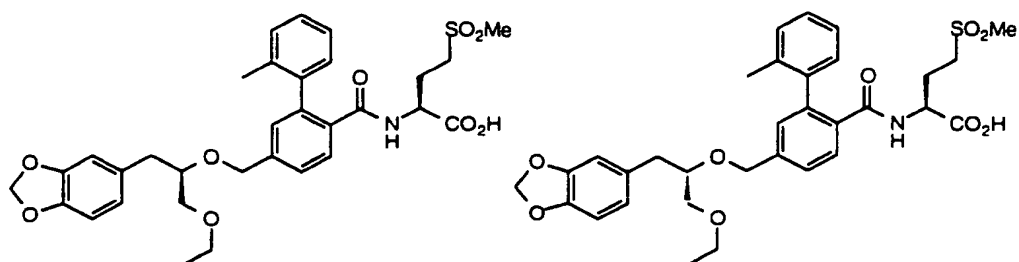


137 138

2305

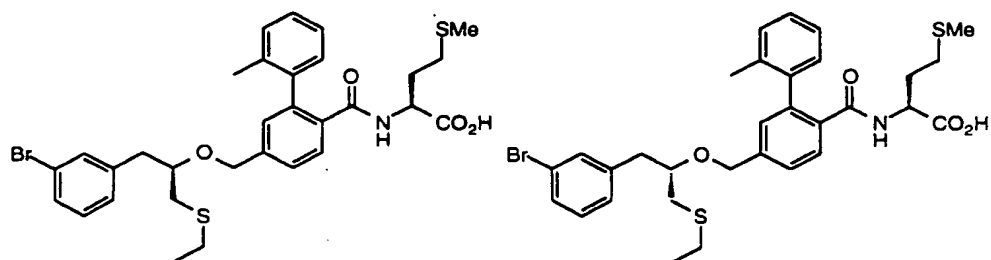


139 140

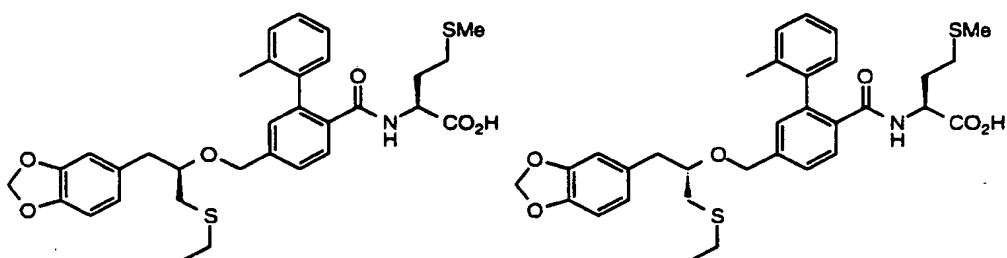


2310

141 142

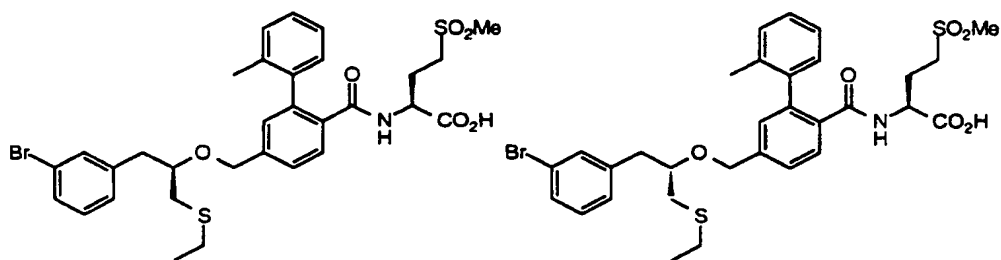


143 144



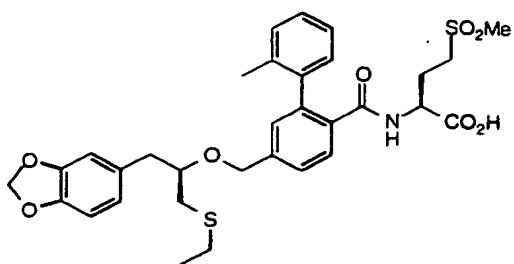
2315

145 146

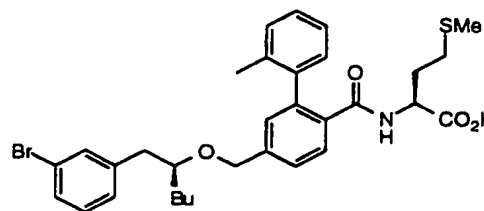
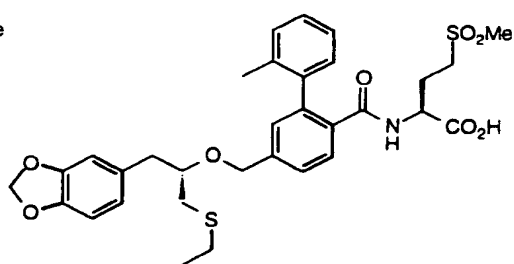


147 148

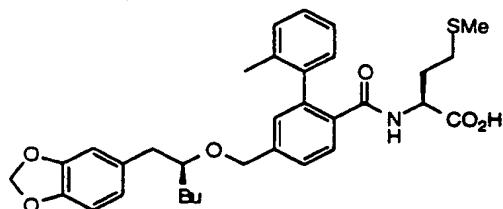
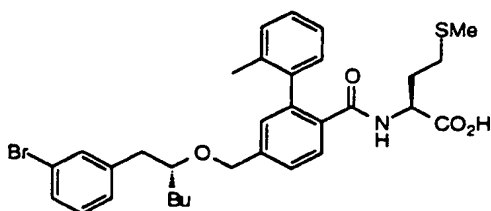
2320



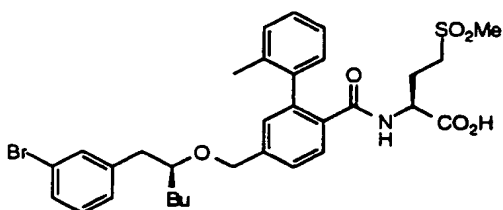
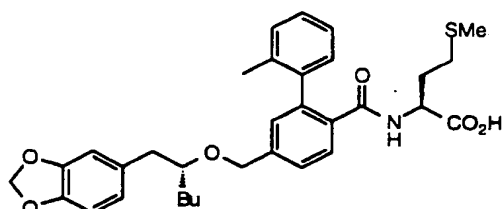
149 150



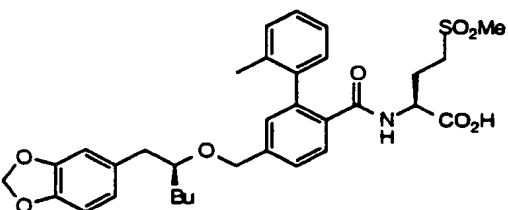
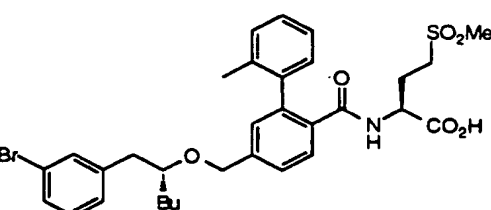
151 152



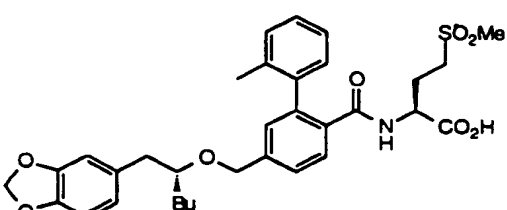
153 154

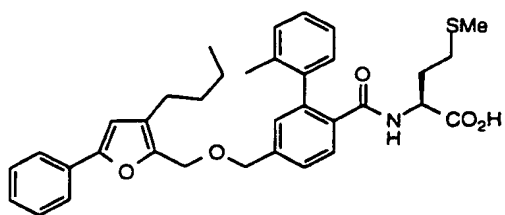
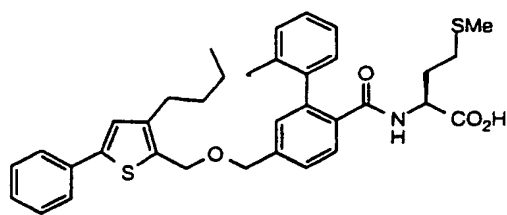
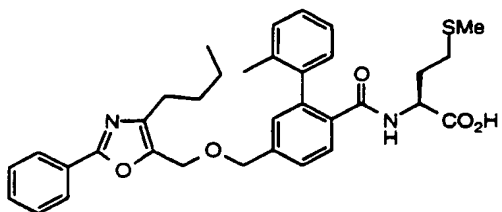
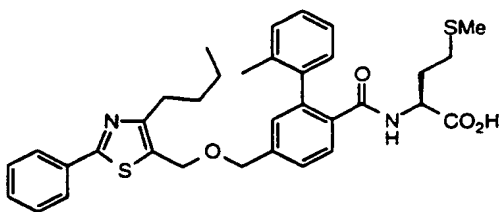
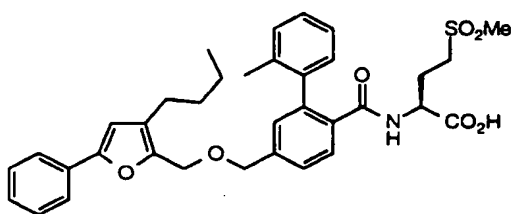
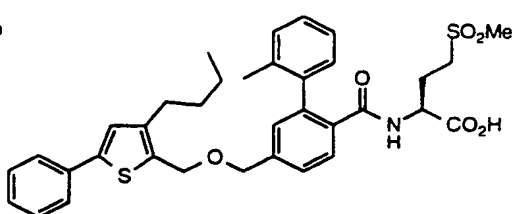
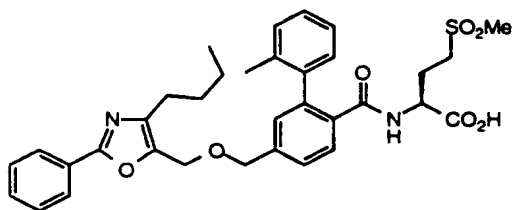
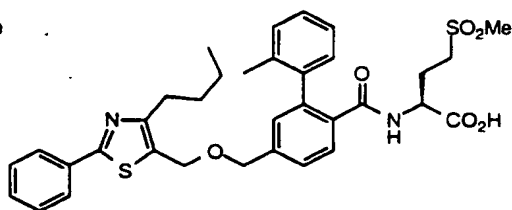
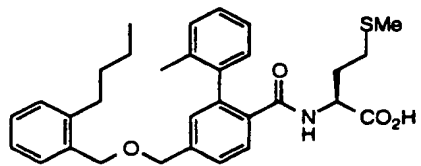
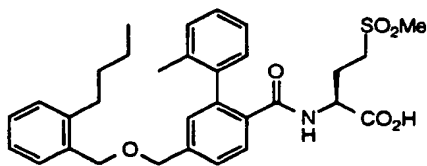


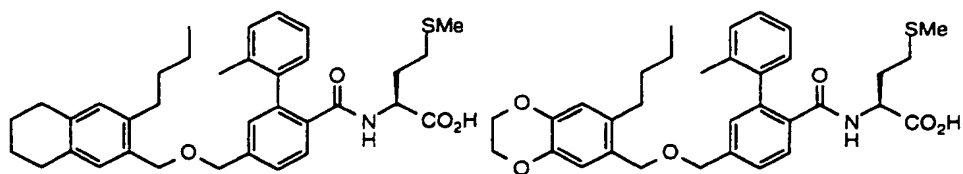
155 156



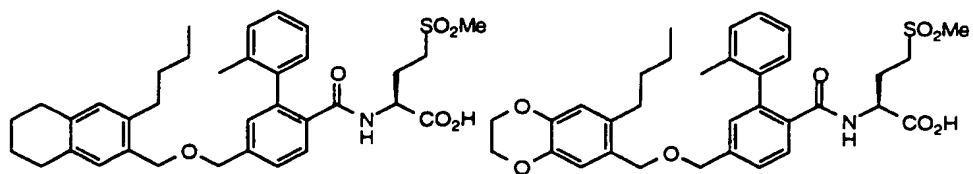
157 158



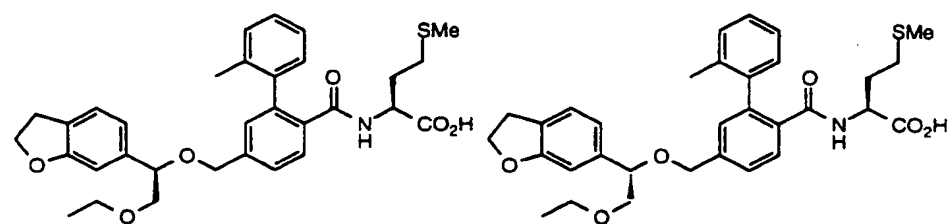
**159****160****161****162****163****164****165****166****167****168**



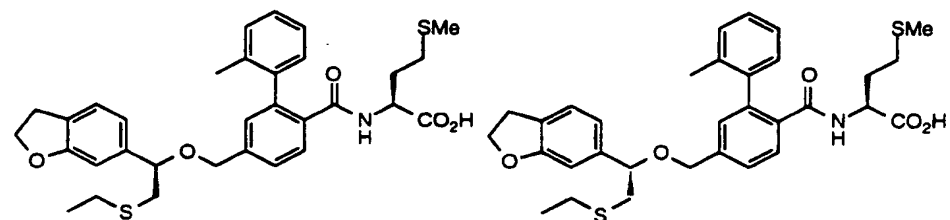
169 170



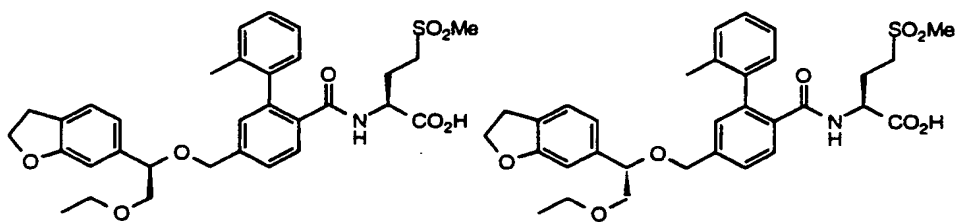
171 172



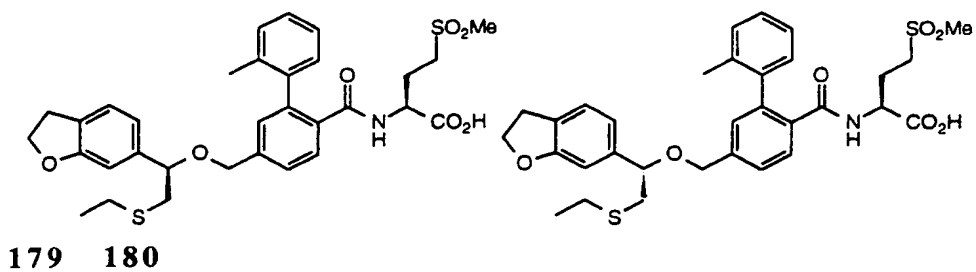
173 174



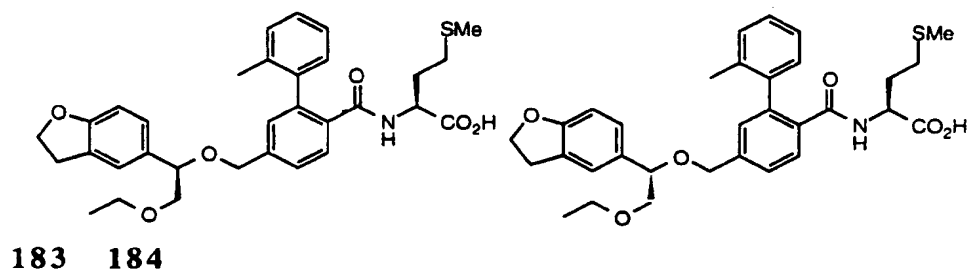
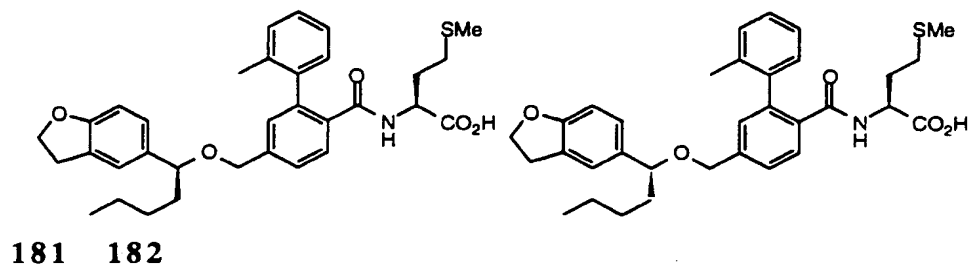
175 176



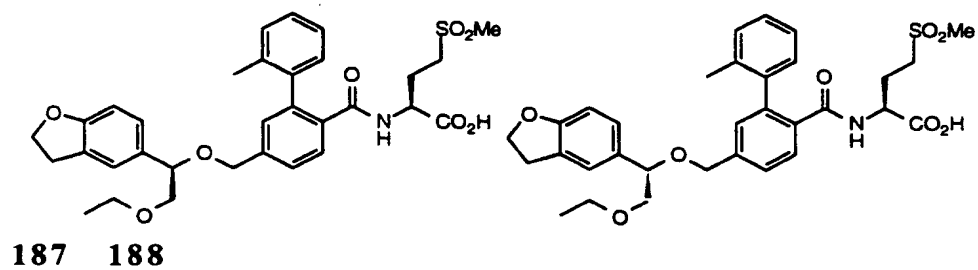
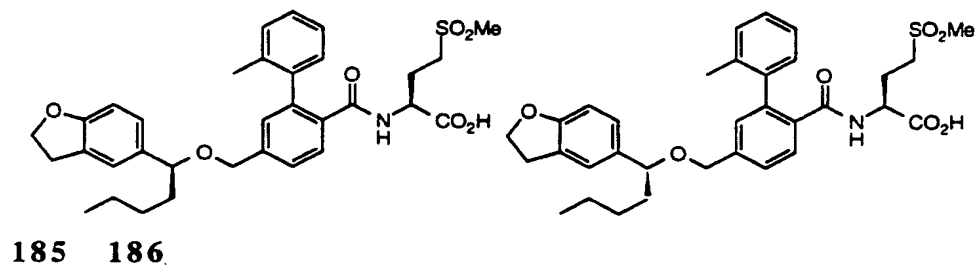
177 178



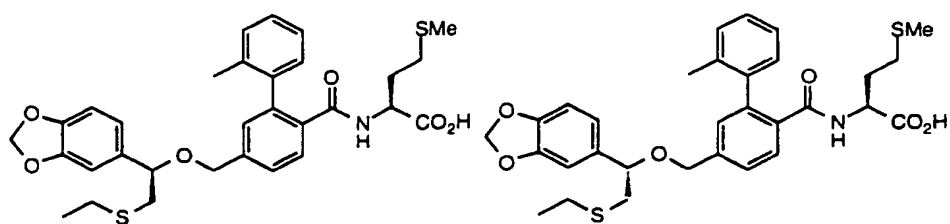
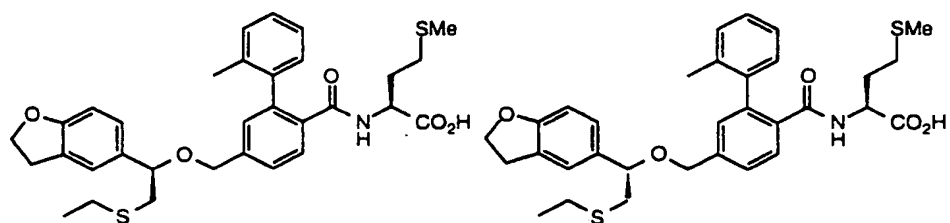
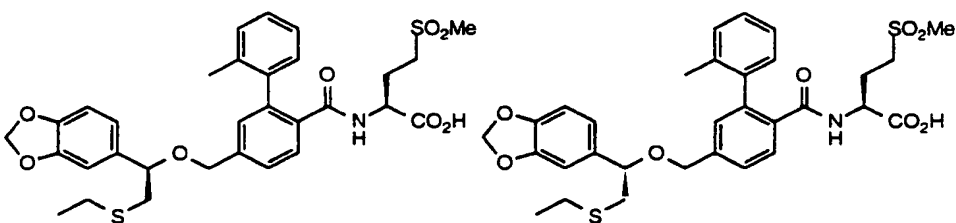
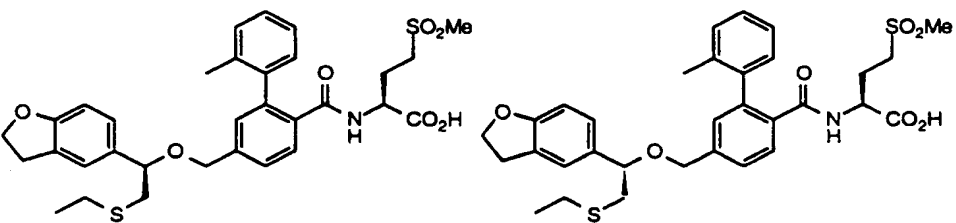
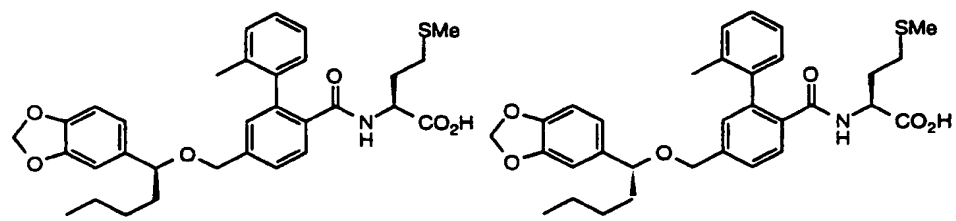
2370

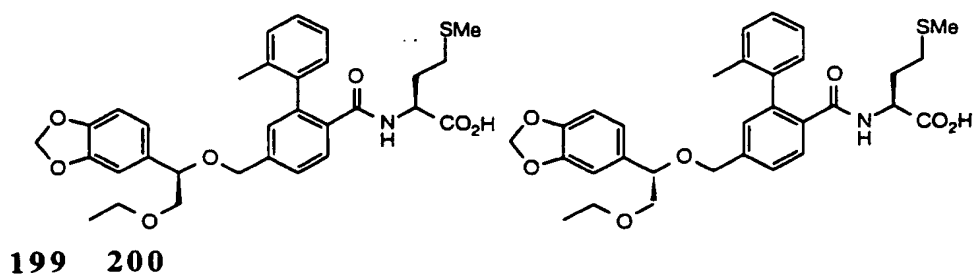


2375

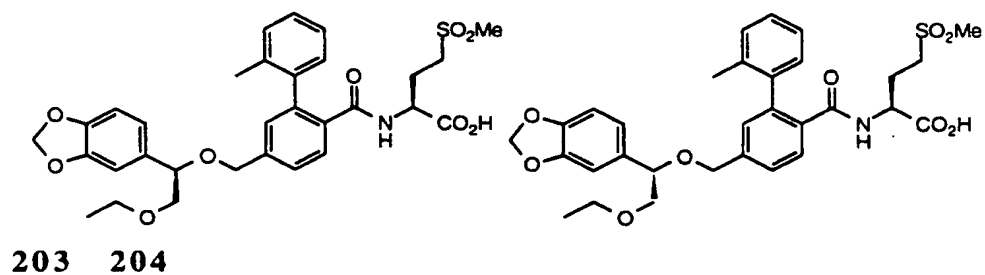
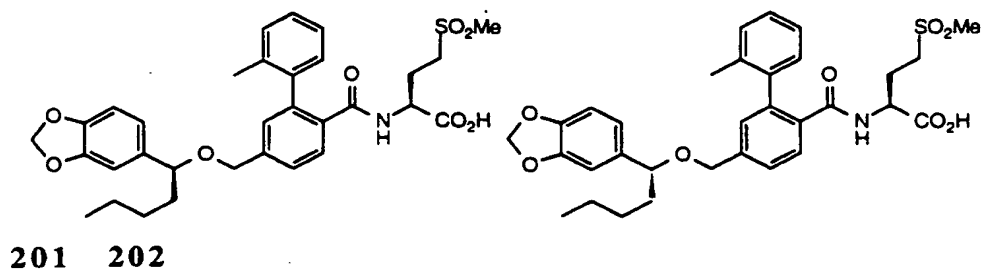


2380

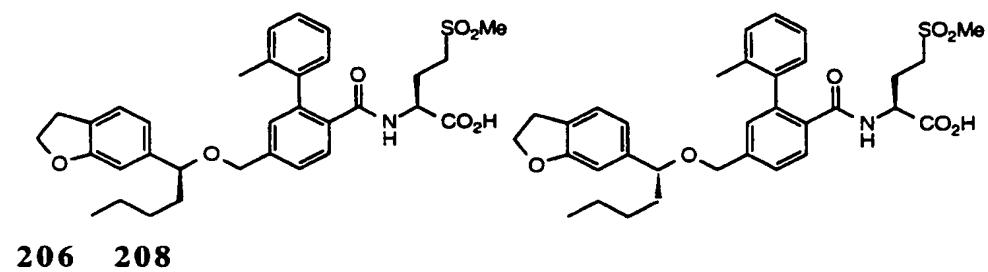
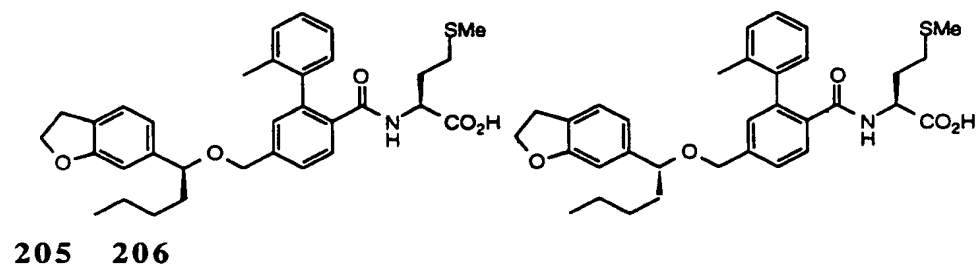
**189 190****191 192****193 194****195 196****197 198**



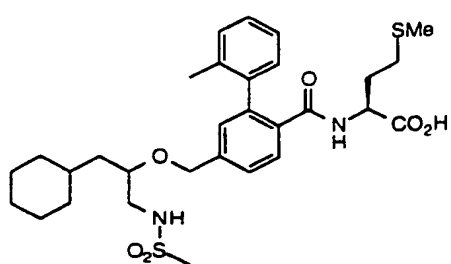
2400



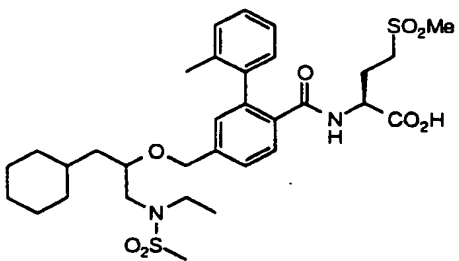
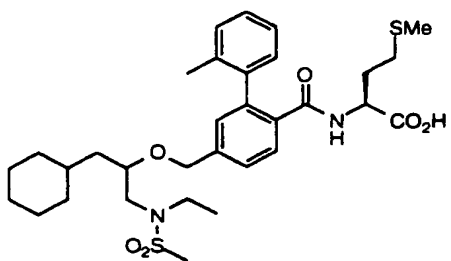
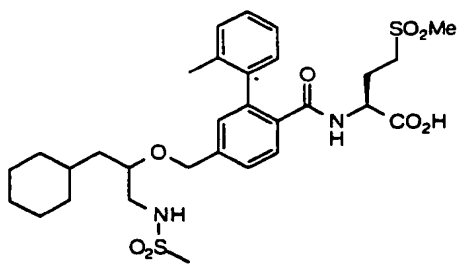
2405



2410

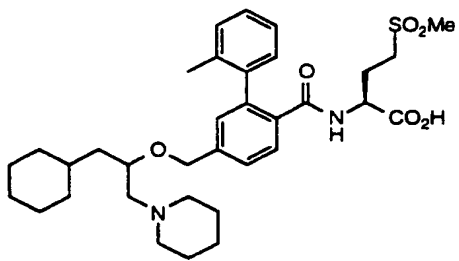
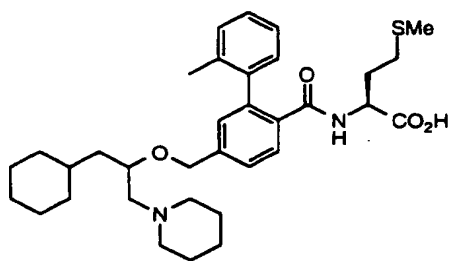


209 210

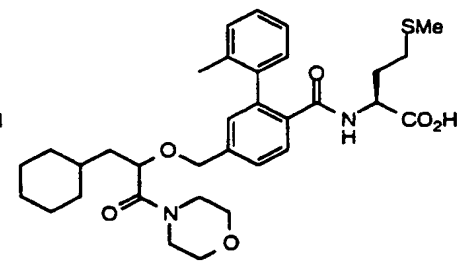
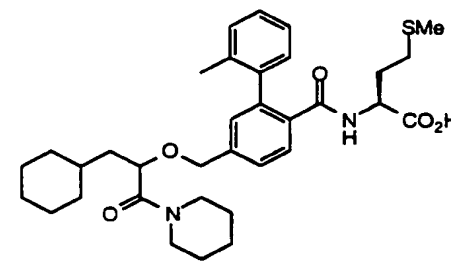


2415

211 212

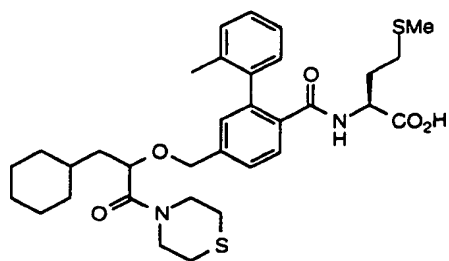


213 214

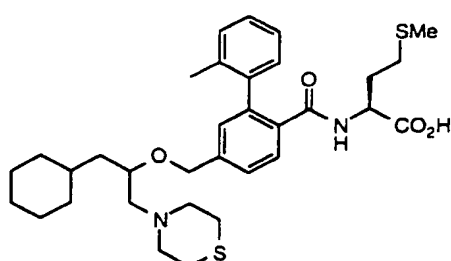


2420

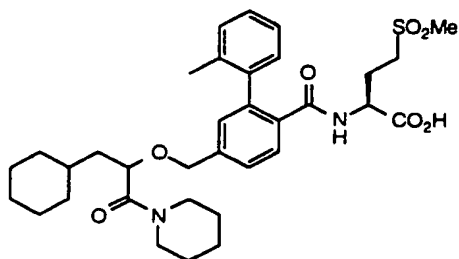
215 216



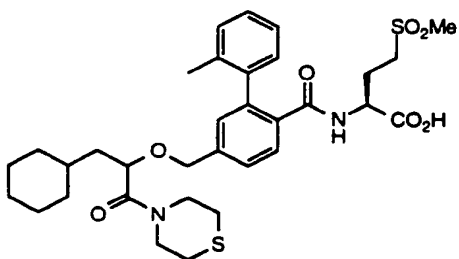
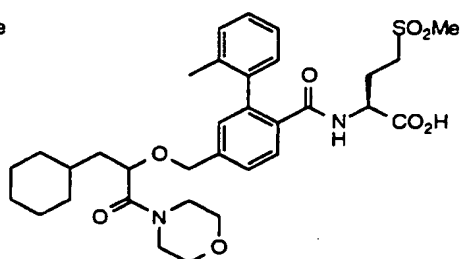
217 218



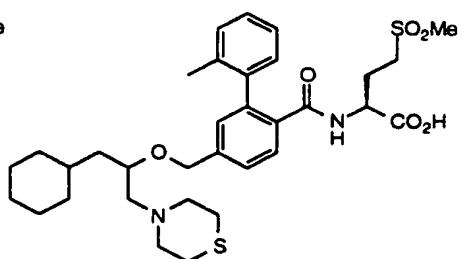
2425



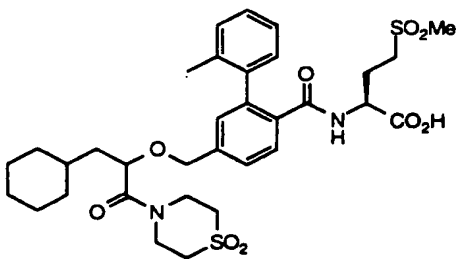
219 220



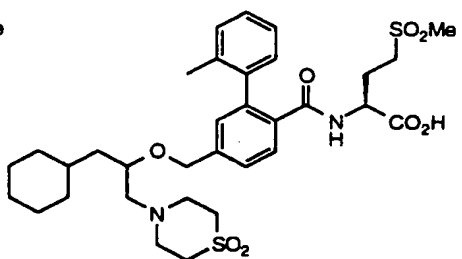
221 222

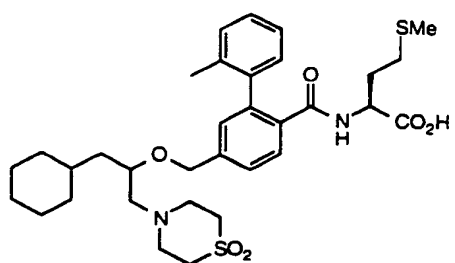
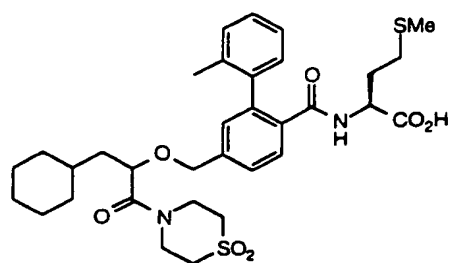


2430



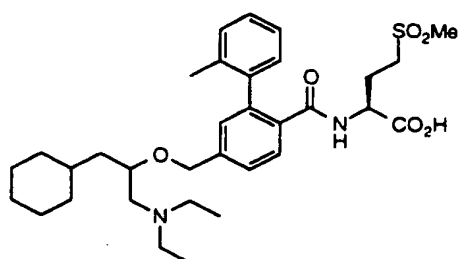
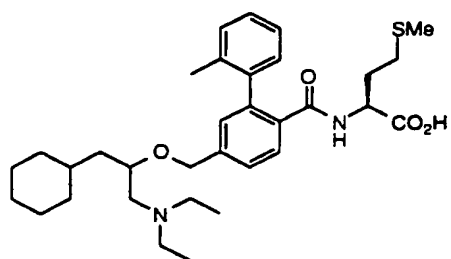
223 224





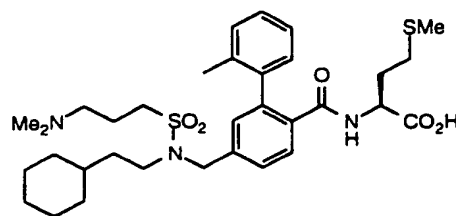
2435

225 226

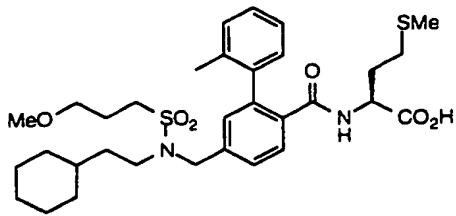


227 228

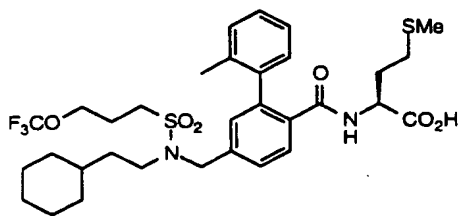
2440

Table 8. Sulfonamides of the Type $ASO_2(B)N-L_1$ 

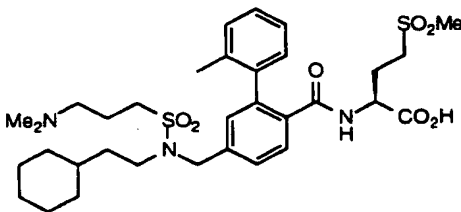
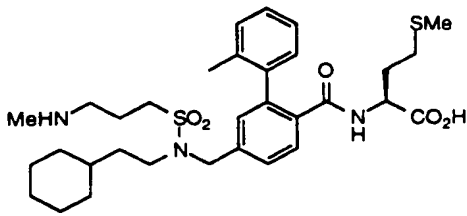
1 2



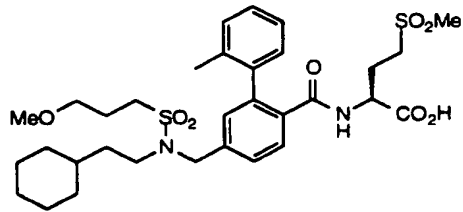
2445



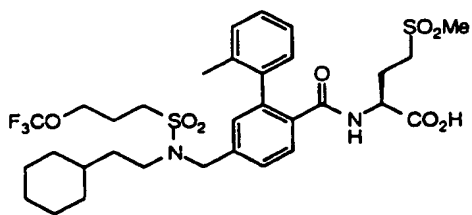
3 4



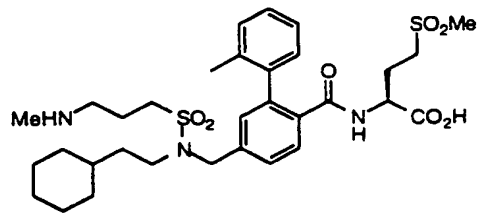
5 6



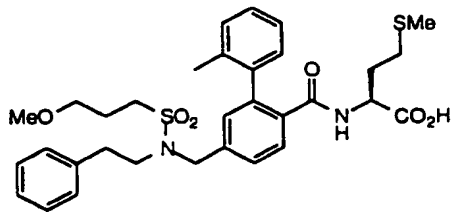
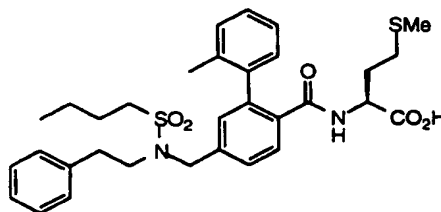
2450



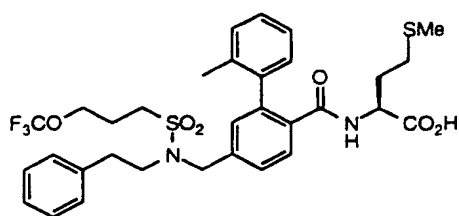
7 8



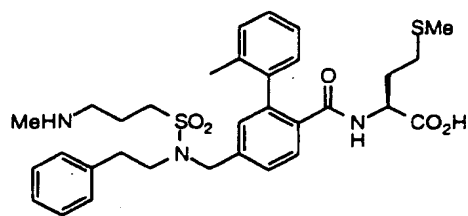
2455



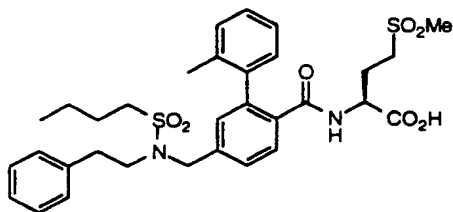
9 10



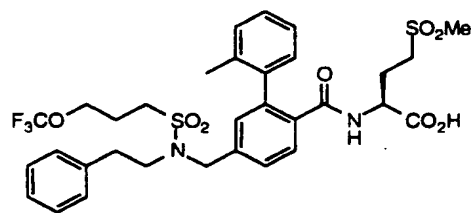
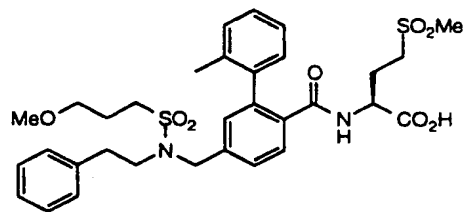
11 12



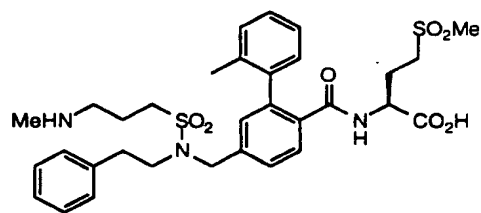
2460



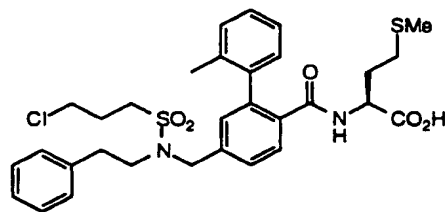
13 14



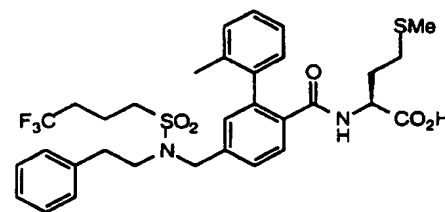
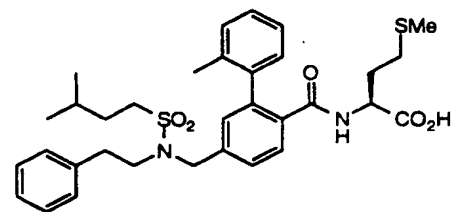
15 16



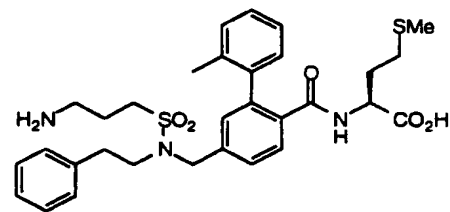
2465



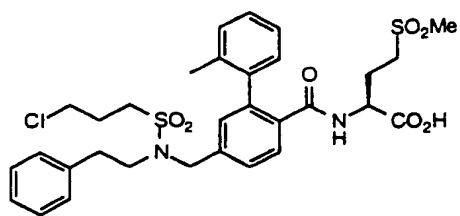
17 18



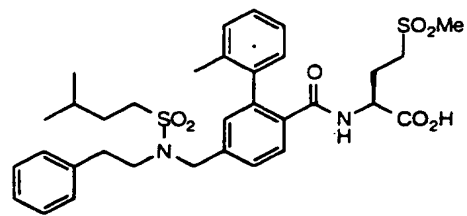
19 20



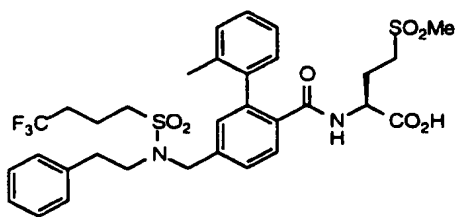
2470



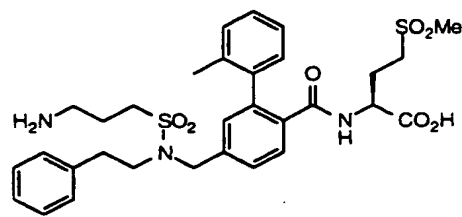
21 22



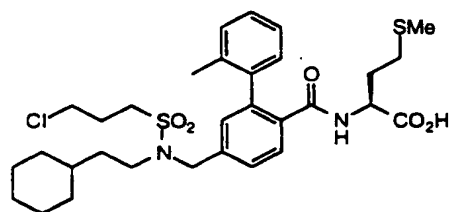
2475



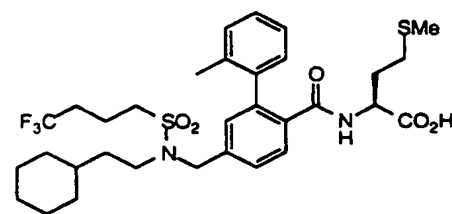
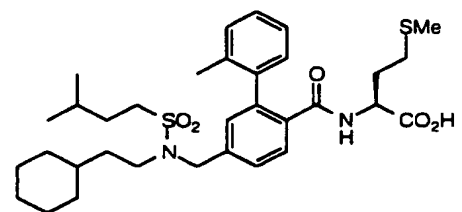
23 24



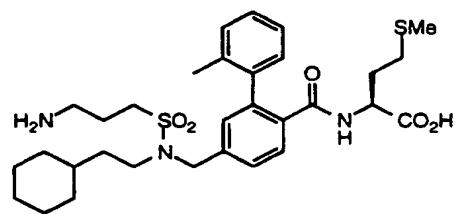
2480



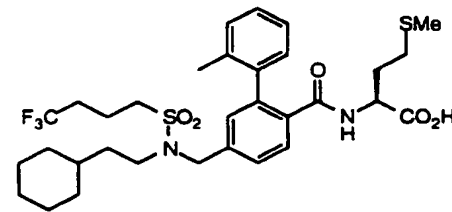
25 26



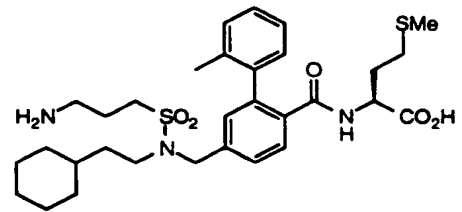
27 28

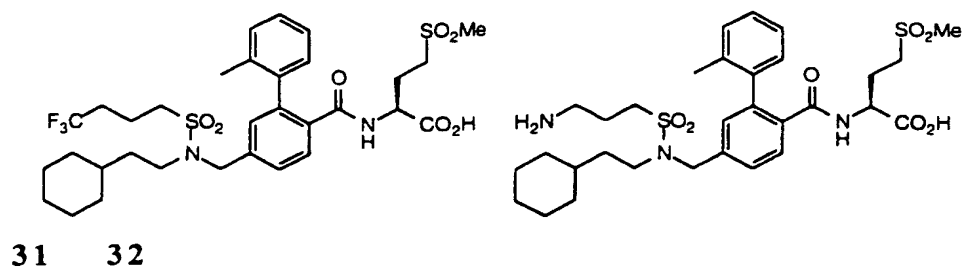


2485

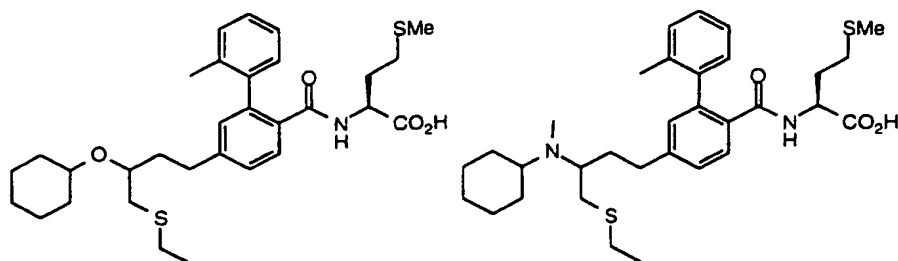


29 30



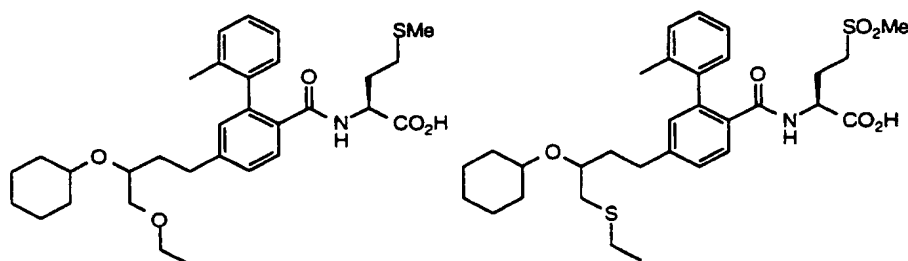


2490

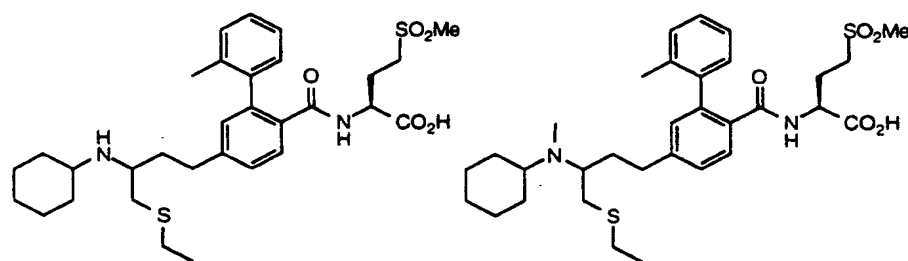
Table 9. Hydrocarbons of the Type A(B)CH₂-L₁

1 2

2495

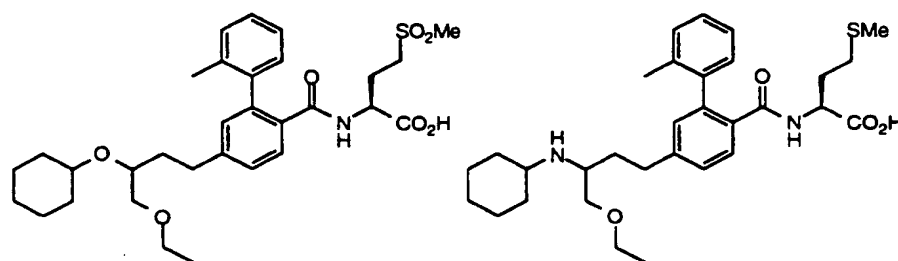


3 4

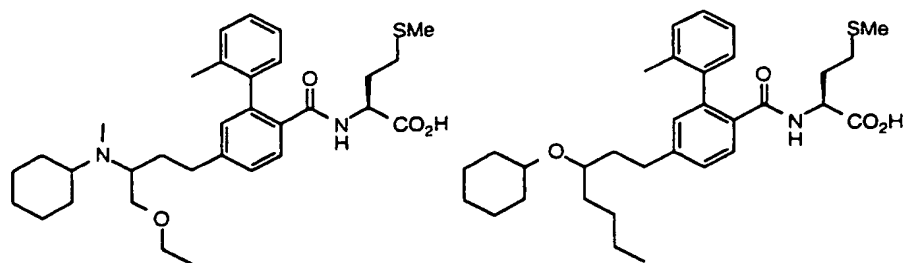


5 6

2500

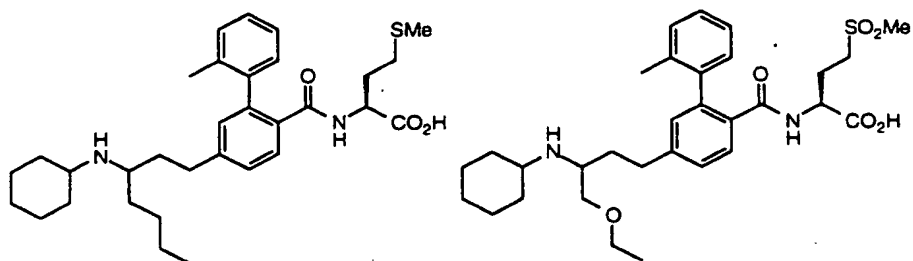


7 8



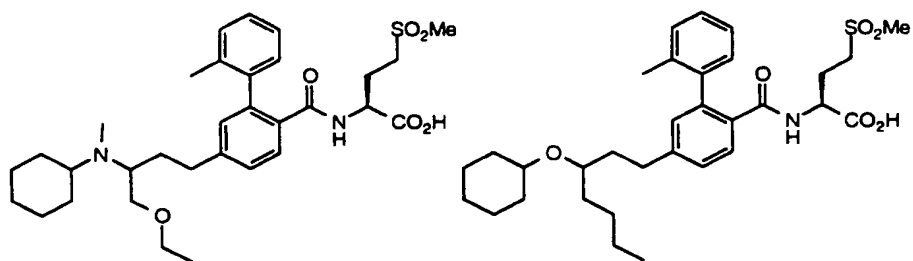
2505

9 10

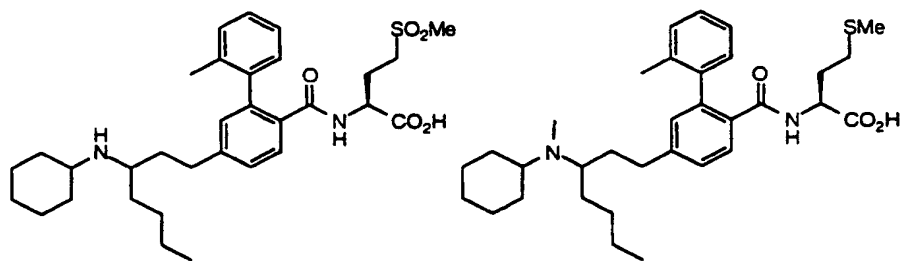


2510

11 12

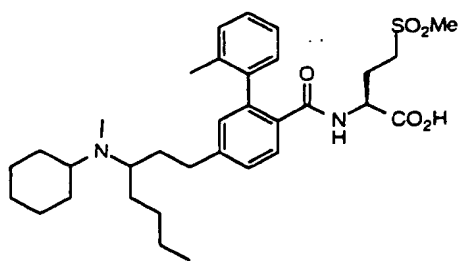


13 14

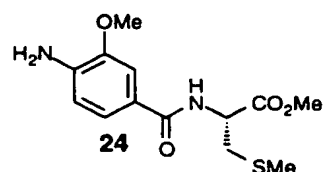
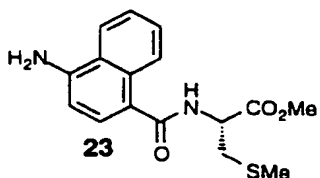
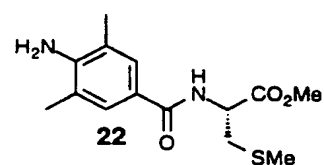
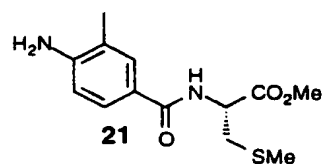
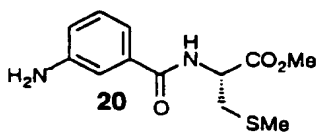
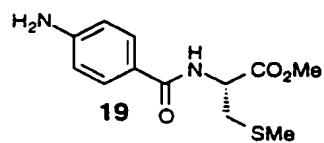
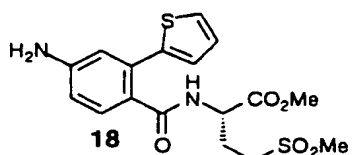
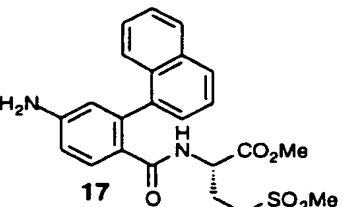
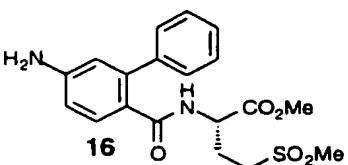
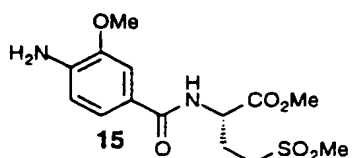
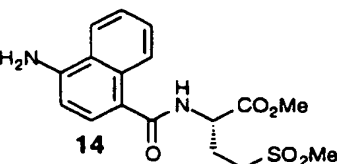
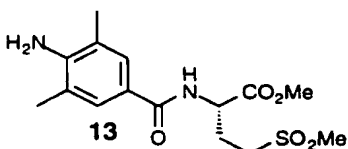
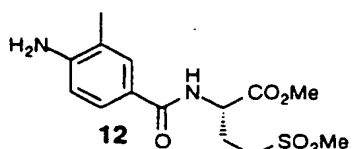
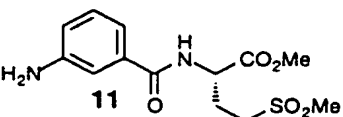
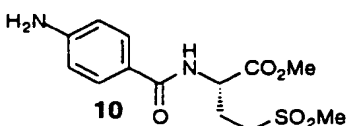
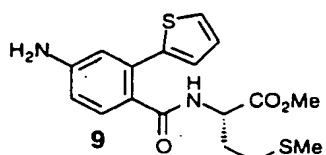
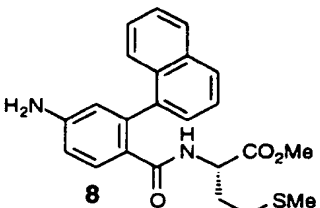
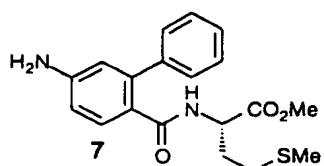
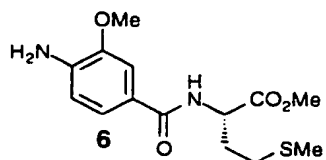
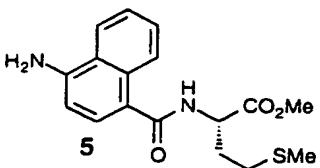
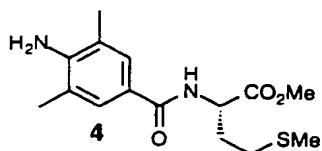
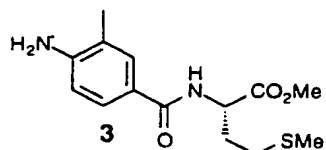
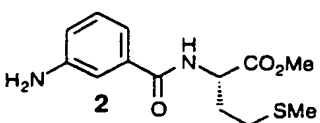
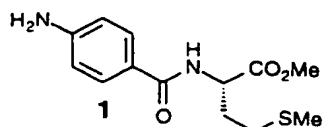


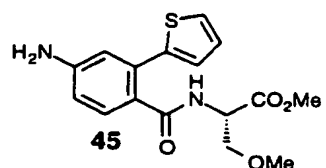
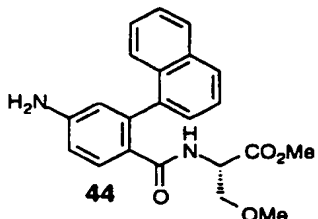
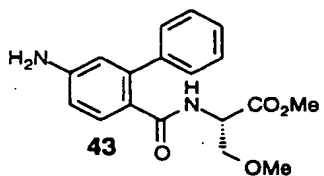
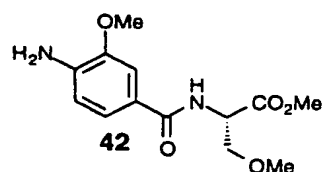
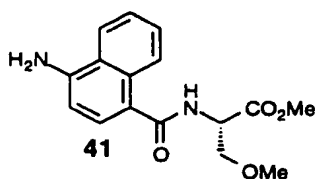
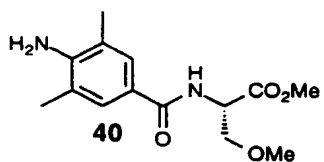
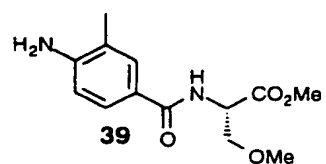
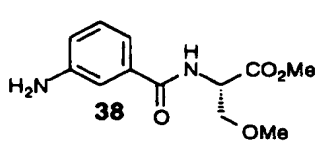
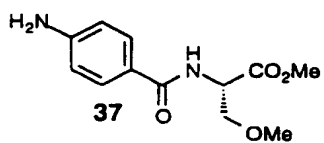
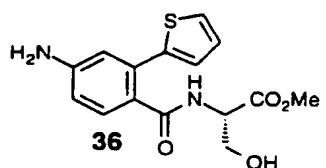
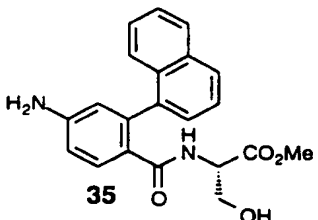
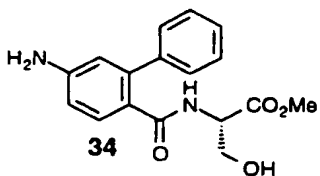
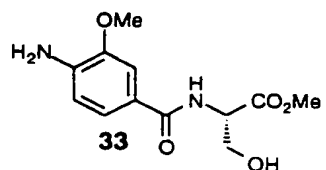
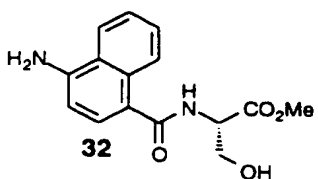
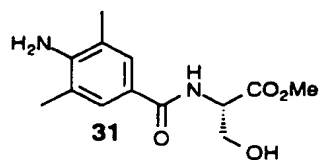
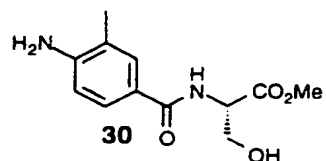
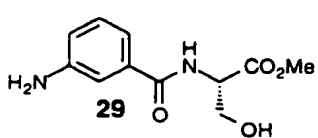
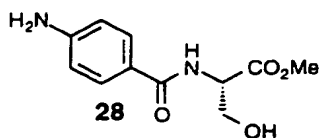
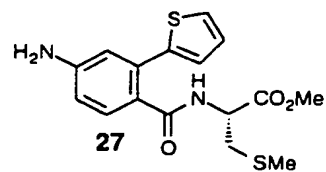
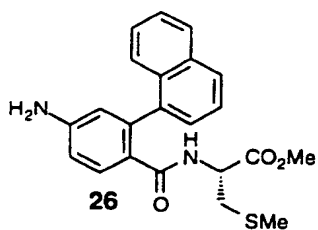
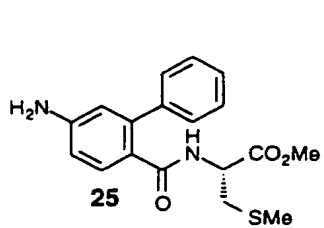
2515

15 16

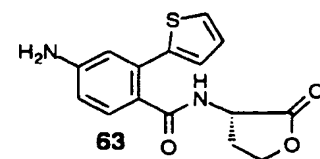
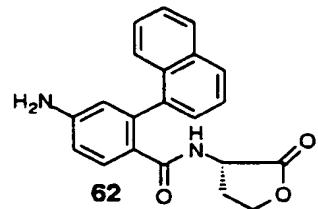
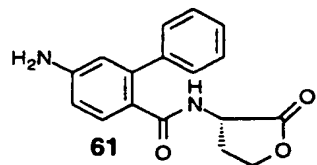
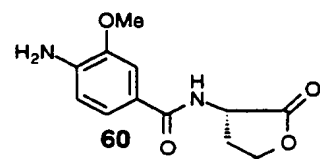
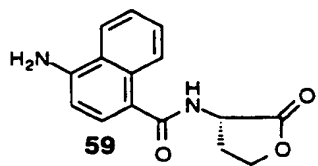
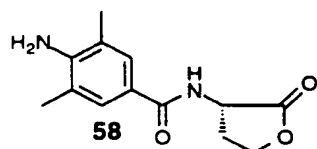
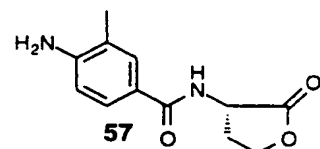
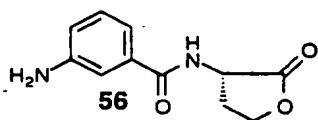
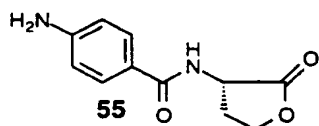
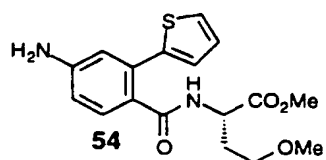
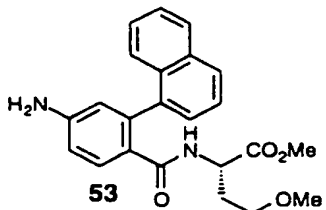
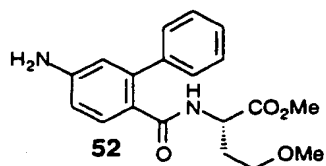
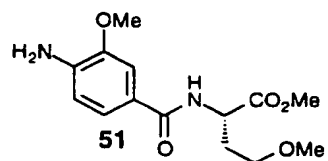
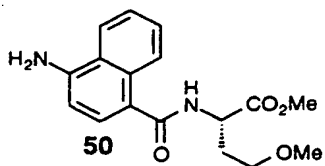
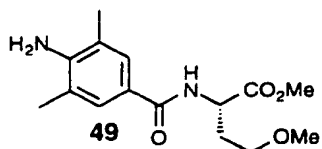
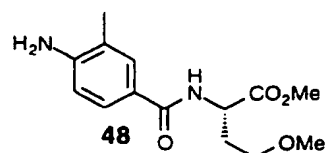
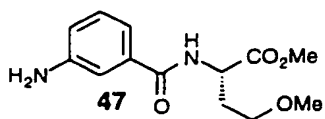
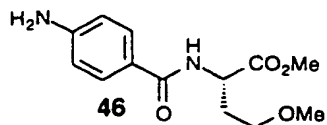


17

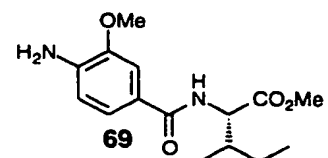
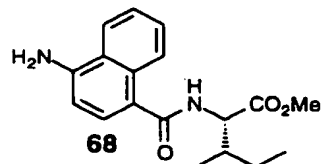
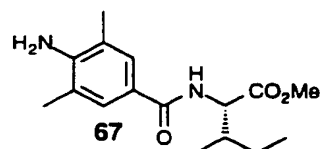
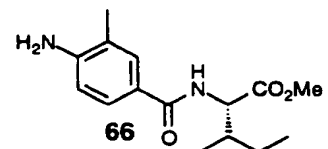
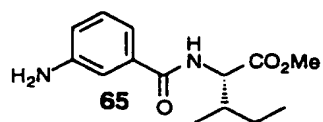
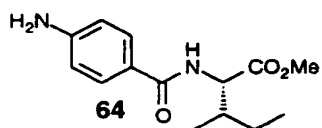
Table 10. Amines of the type B-NH₂

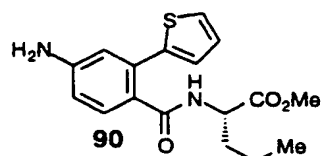
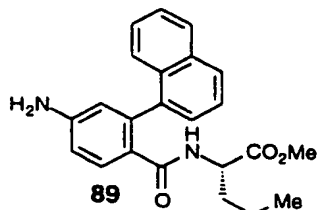
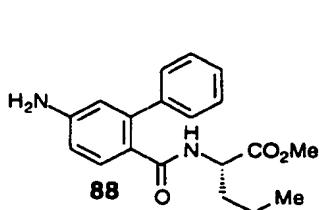
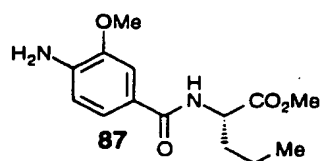
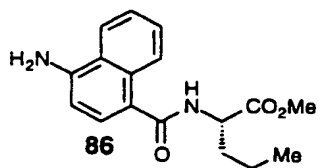
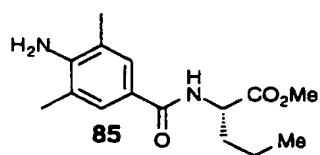
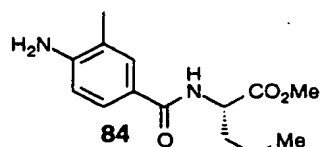
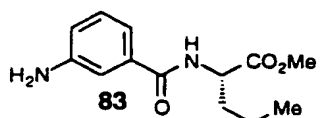
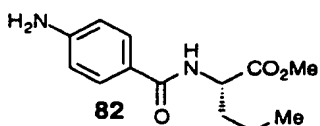
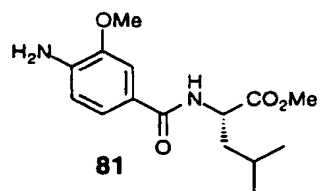
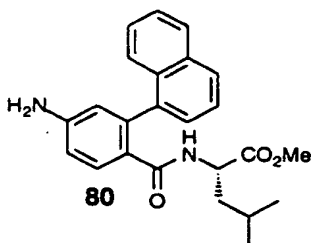
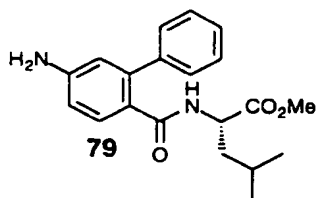
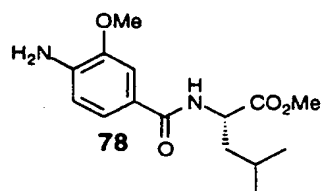
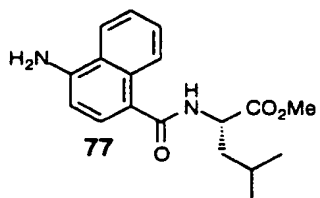
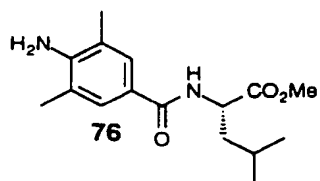
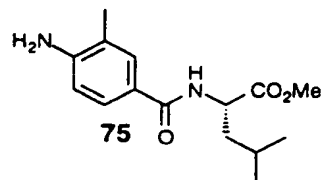
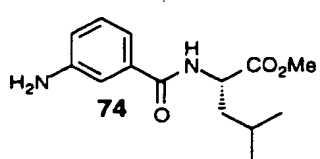
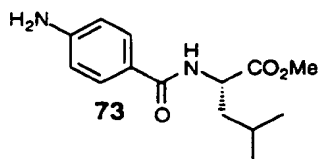
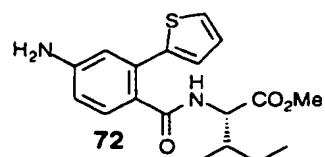
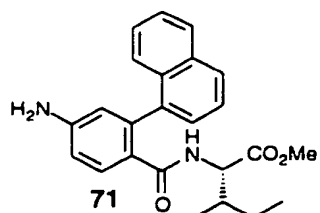
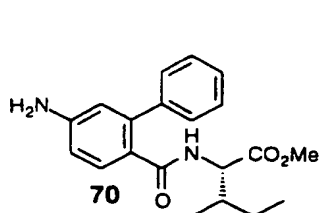


2535

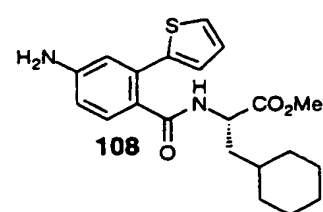
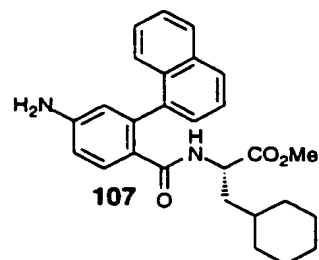
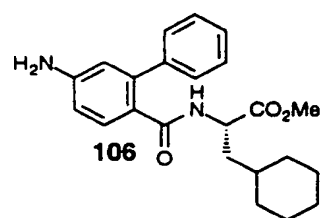
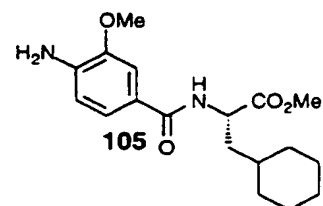
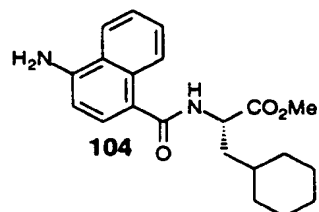
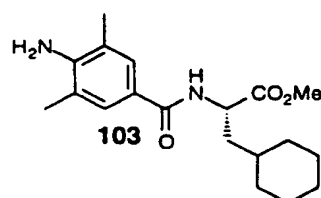
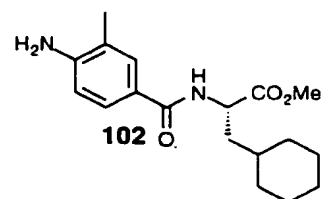
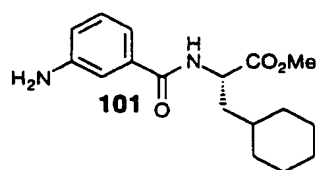
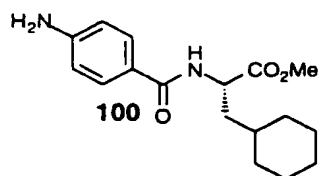
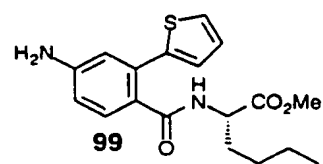
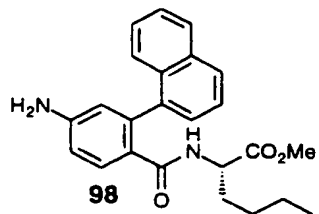
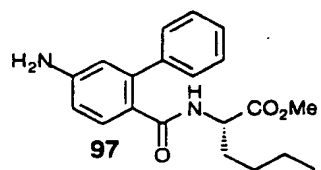
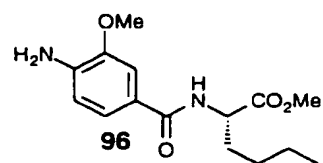
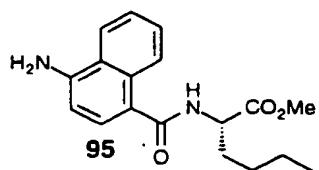
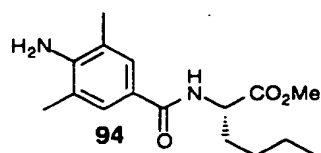
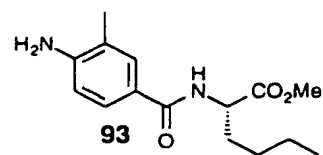
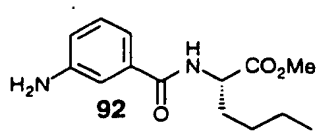
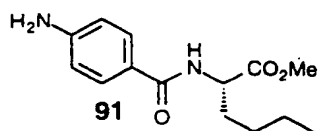


2540

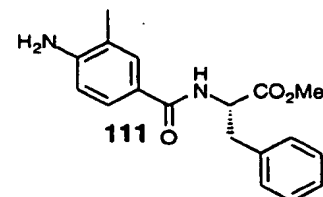
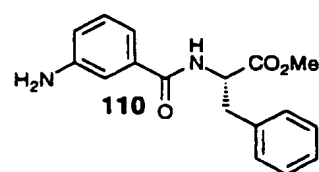
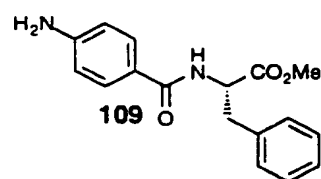


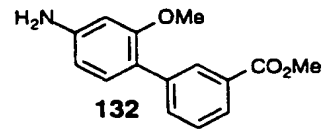
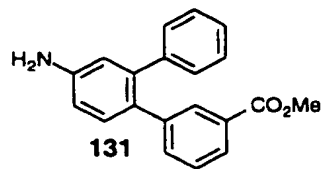
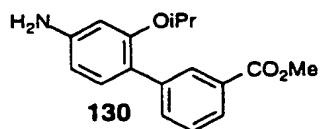
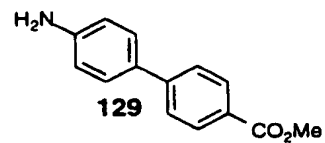
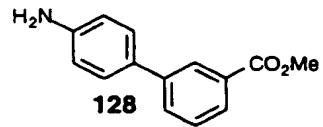
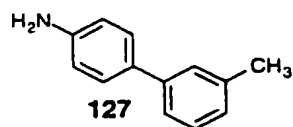
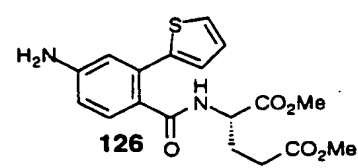
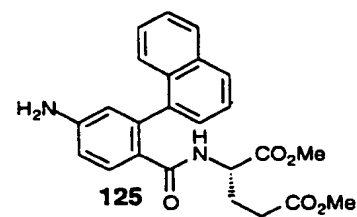
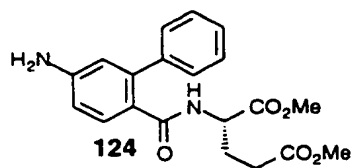
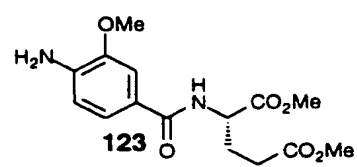
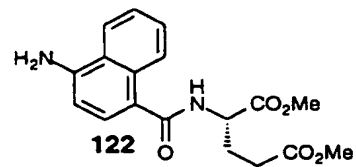
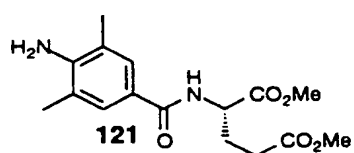
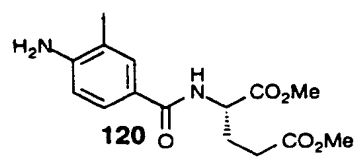
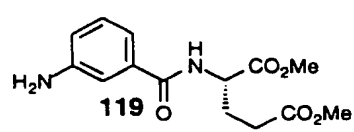
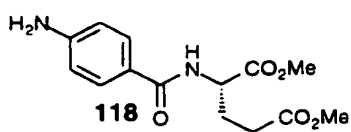
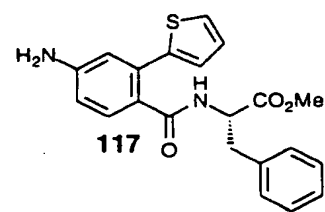
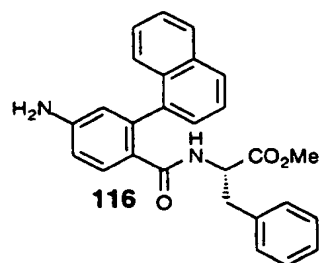
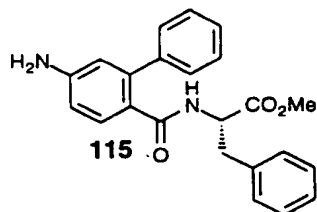
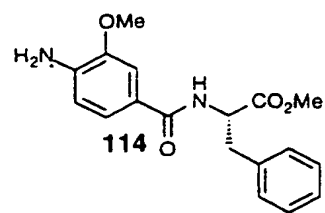
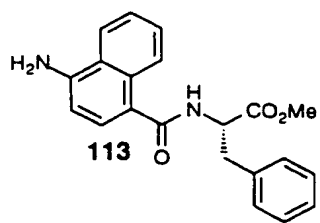
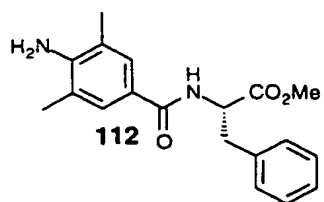


2550

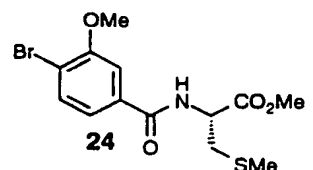
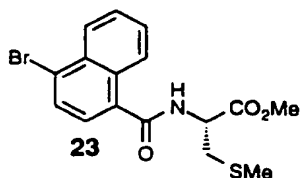
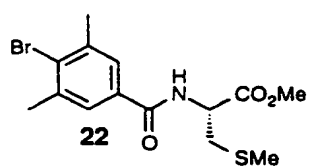
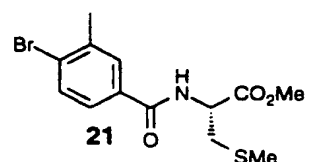
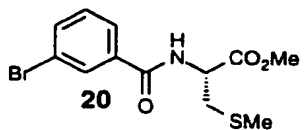
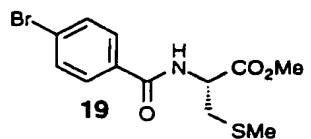
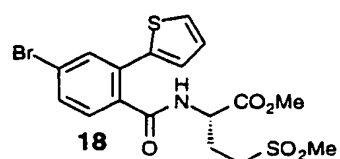
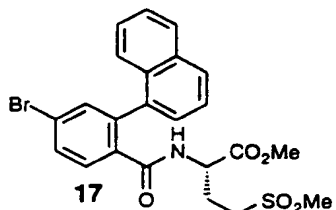
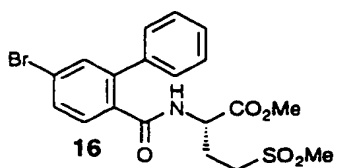
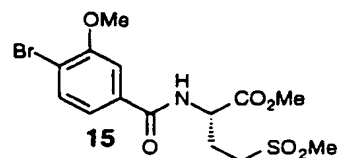
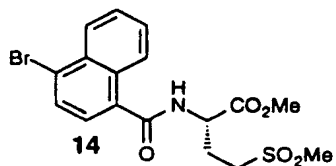
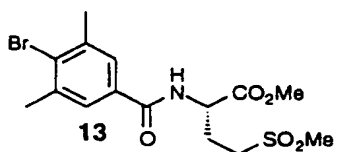
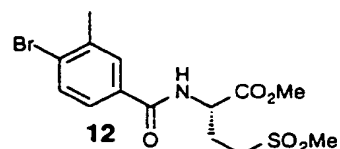
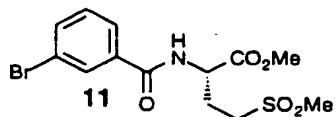
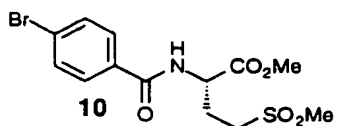
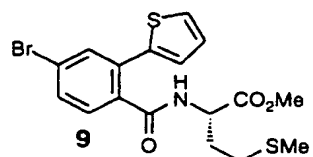
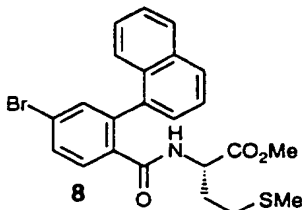
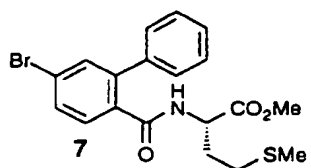
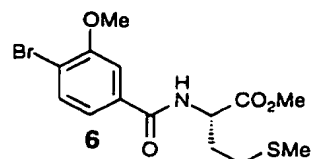
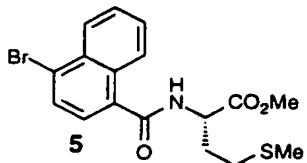
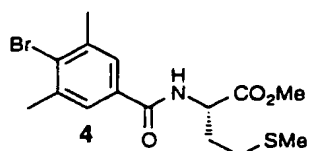
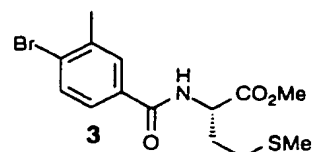
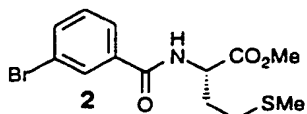
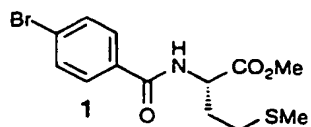


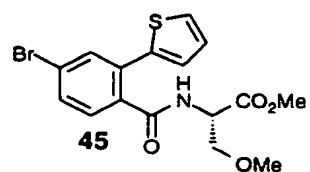
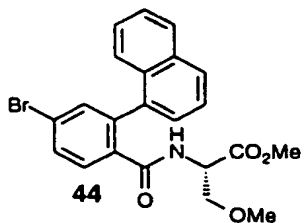
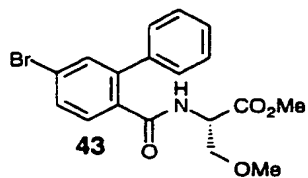
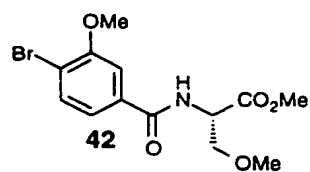
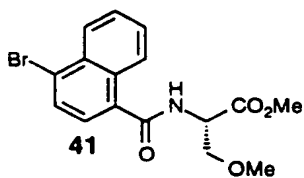
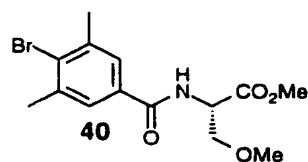
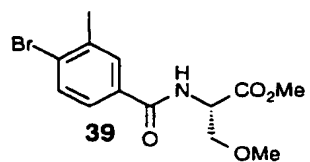
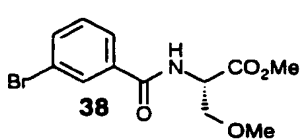
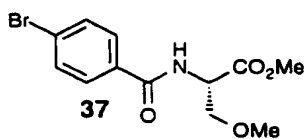
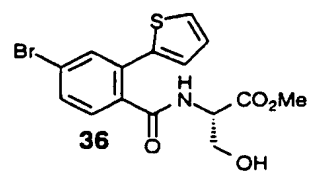
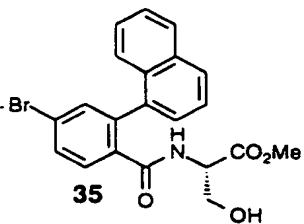
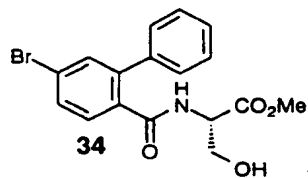
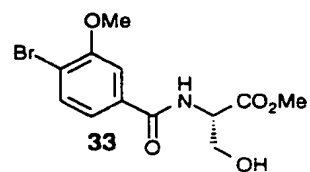
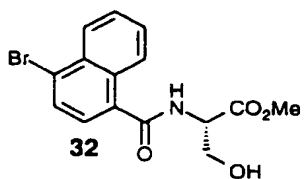
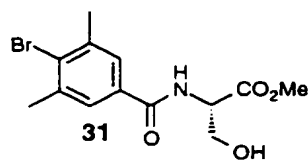
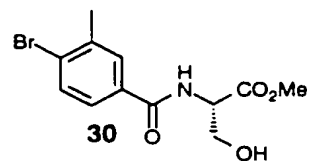
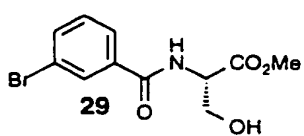
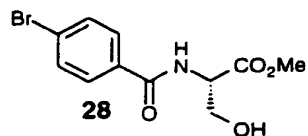
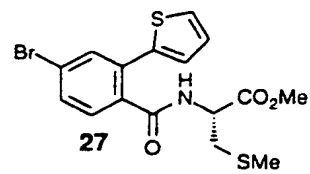
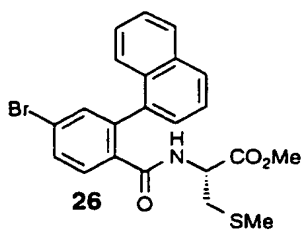
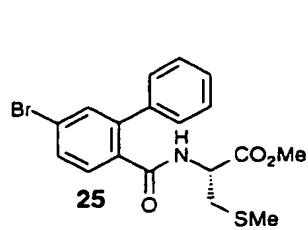
2555

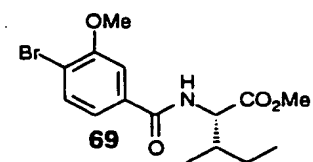
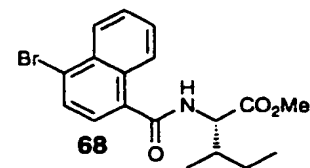
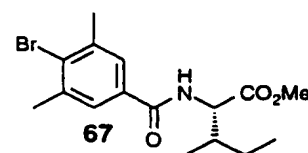
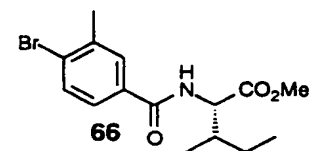
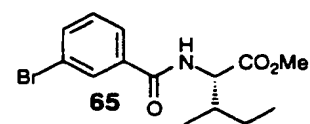
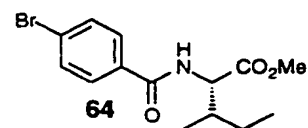
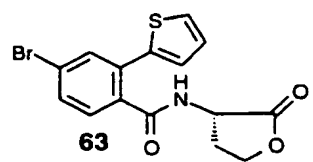
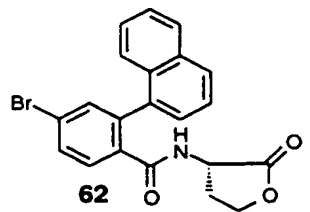
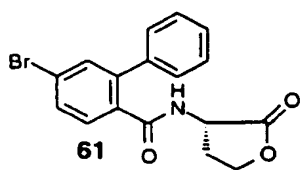
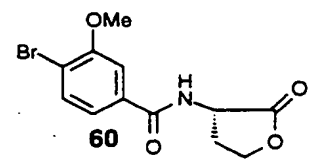
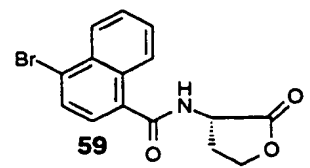
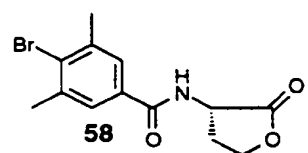
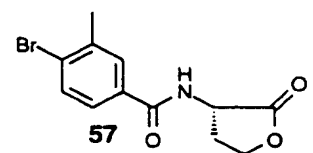
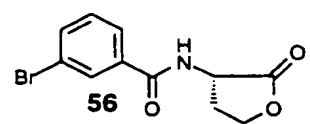
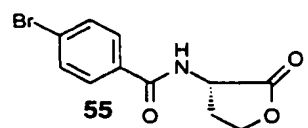
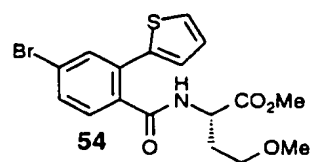
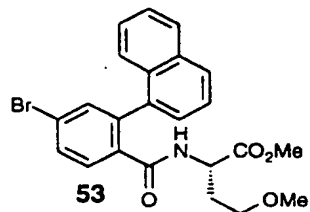
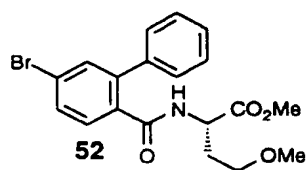
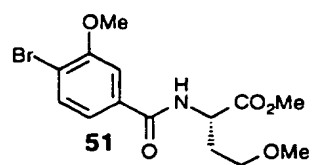
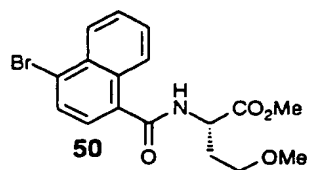
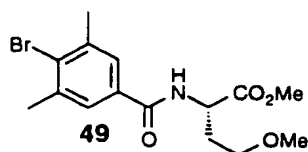
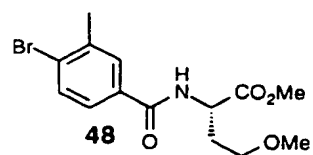
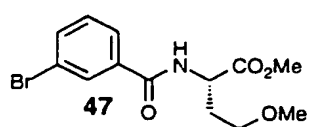
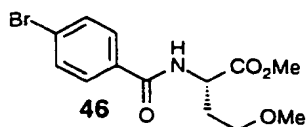




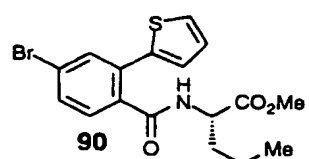
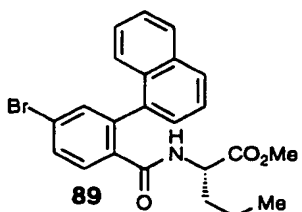
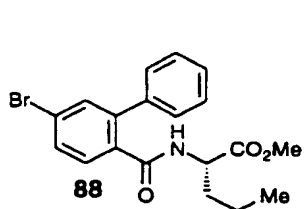
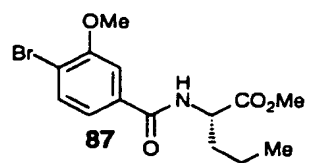
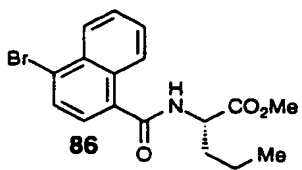
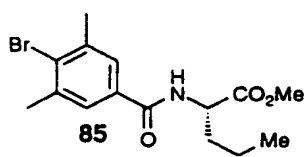
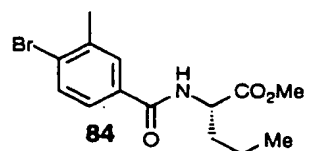
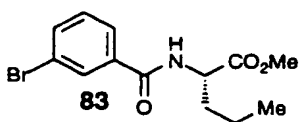
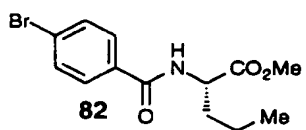
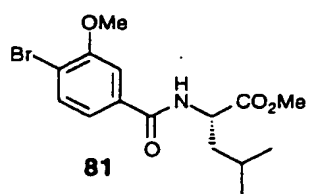
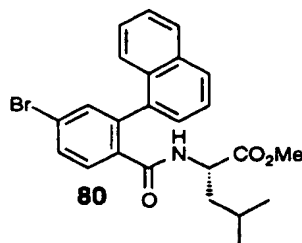
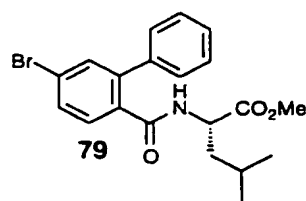
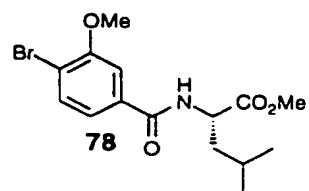
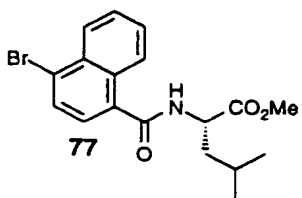
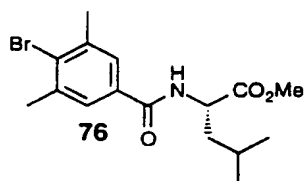
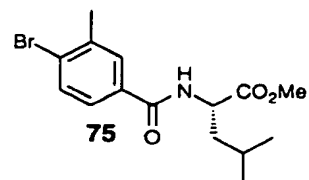
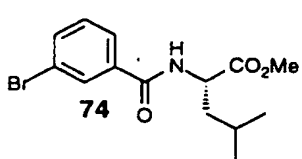
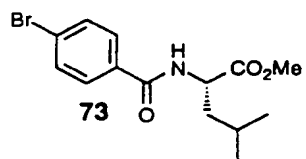
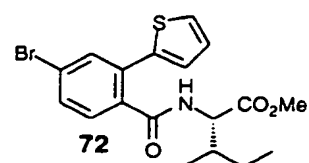
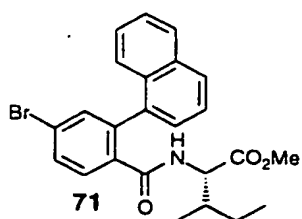
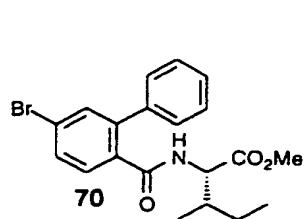
2565 Table 11. Bromides of the type B-Br

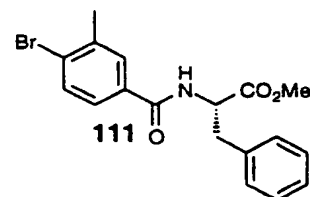
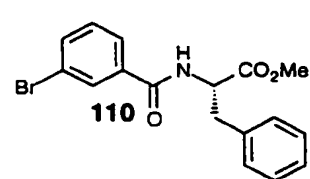
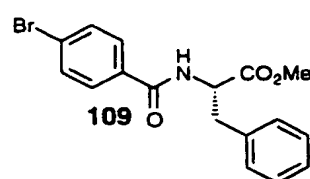
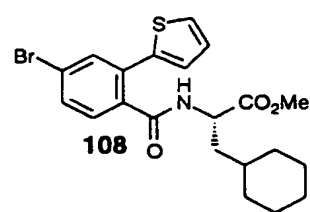
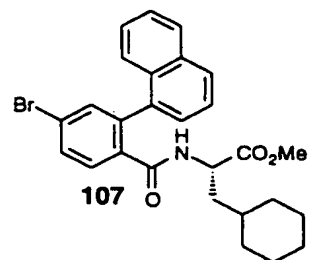
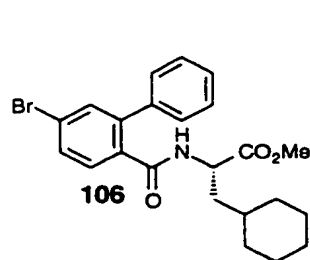
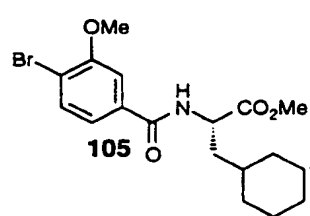
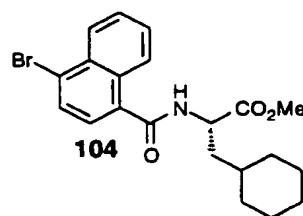
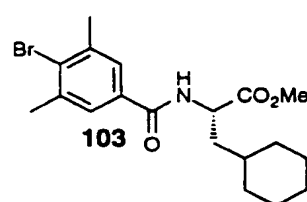
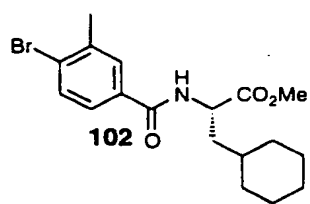
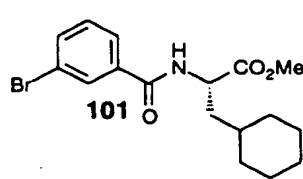
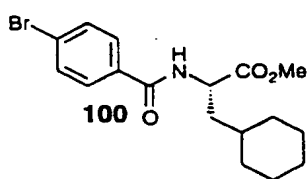
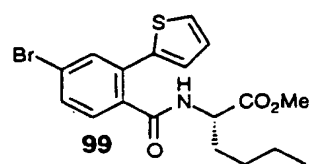
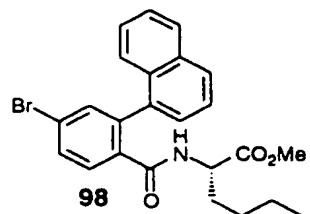
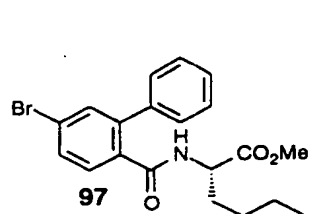
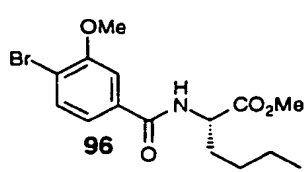
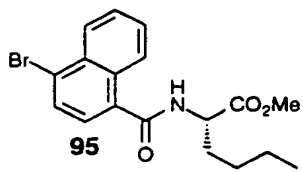
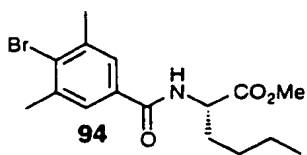
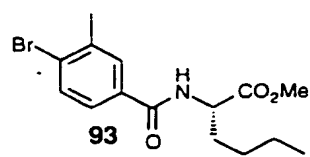
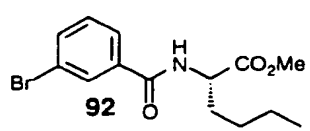
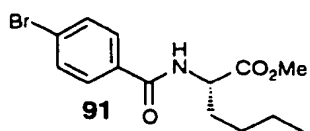




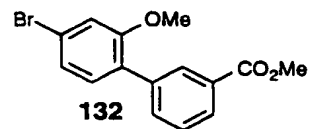
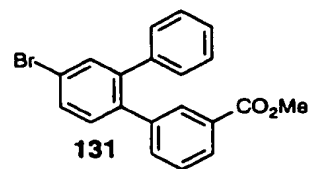
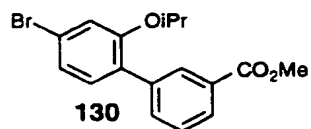
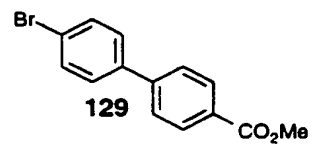
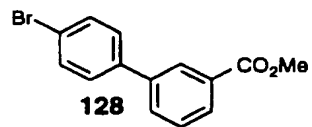
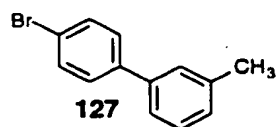
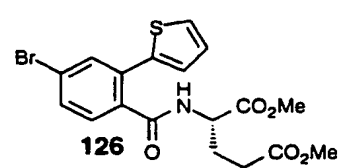
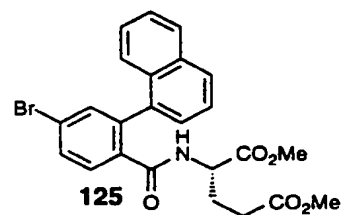
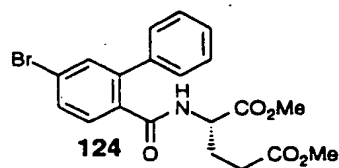
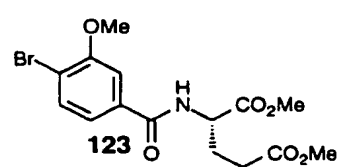
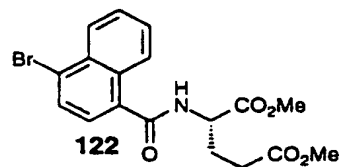
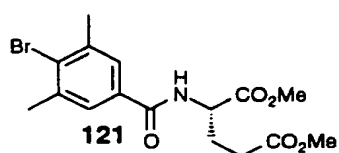
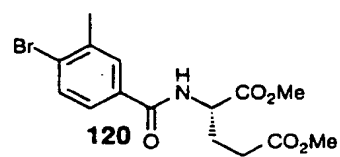
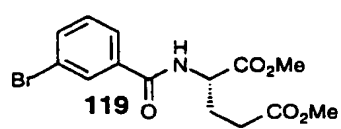
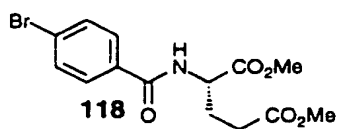
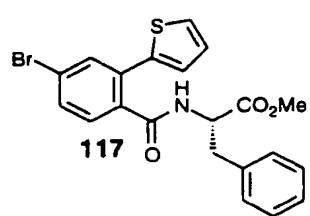
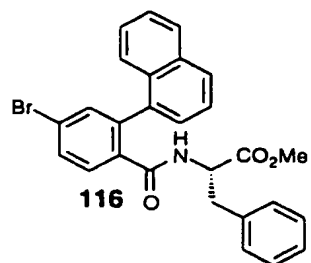
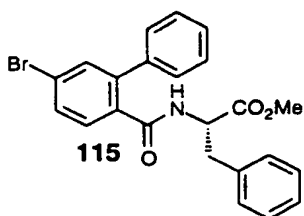
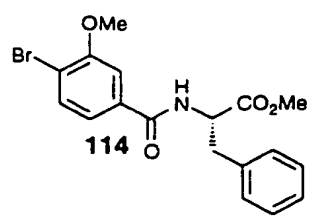
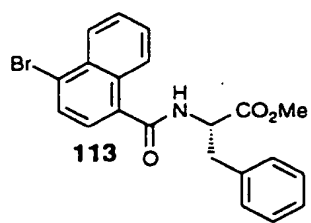
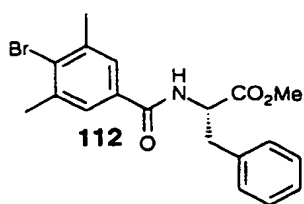


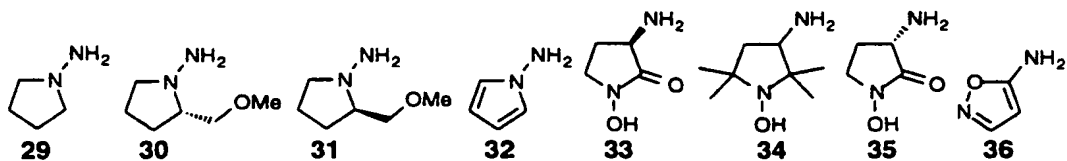
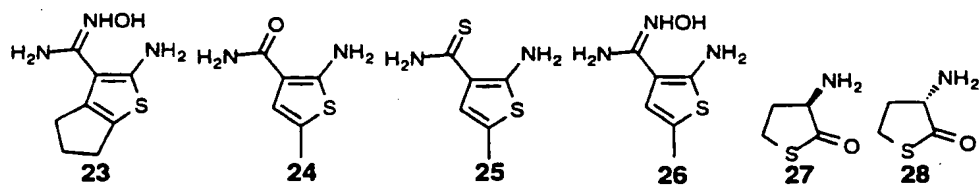
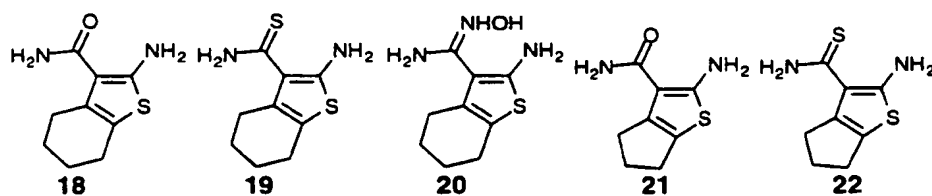
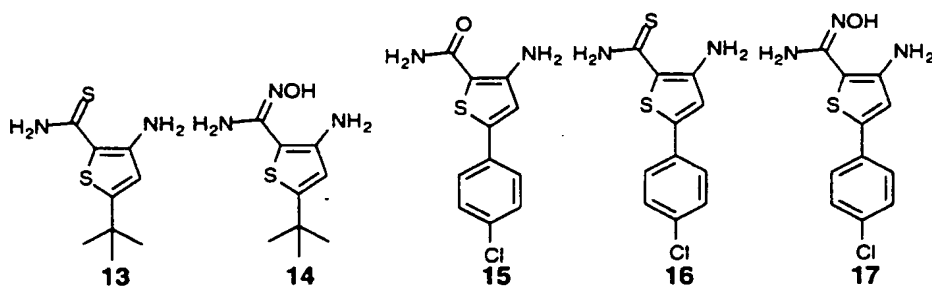
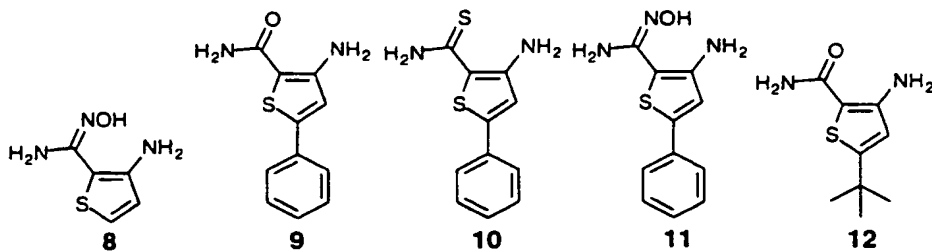
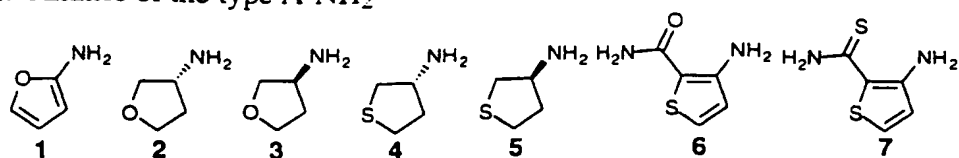
2585

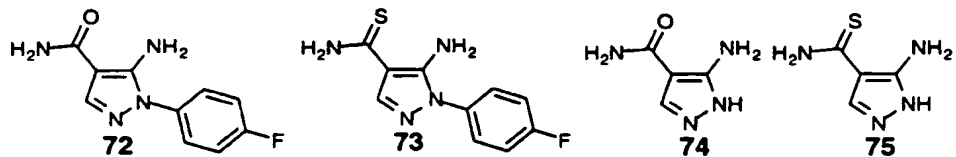
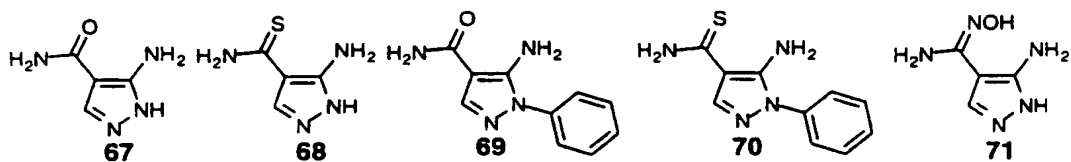
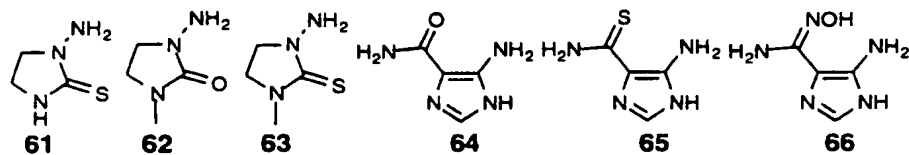
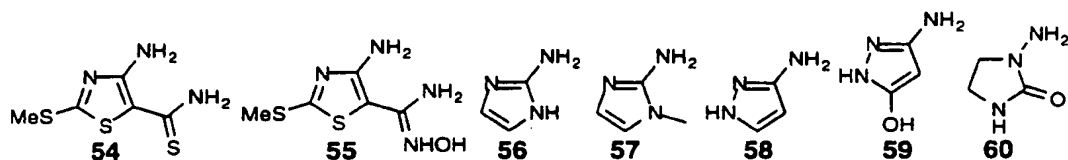
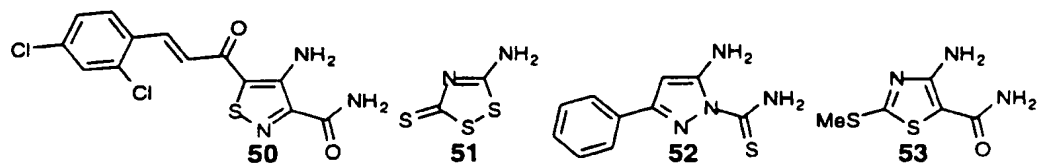
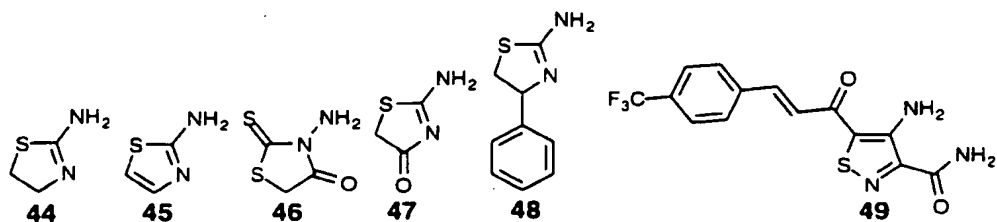
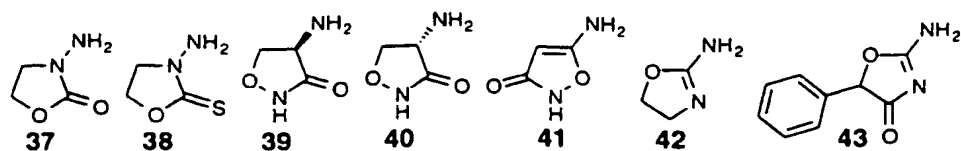


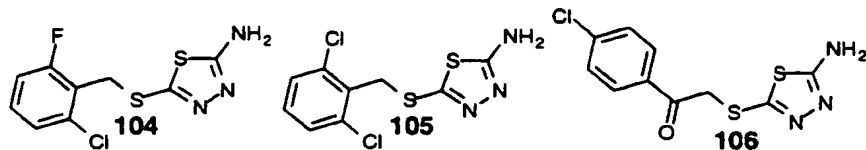
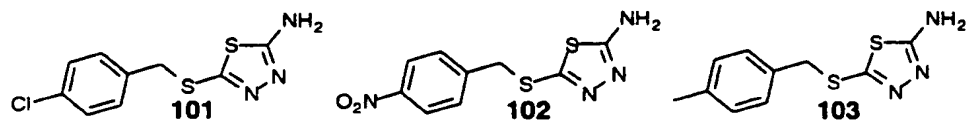
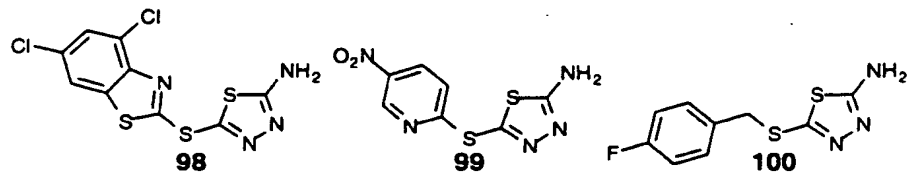
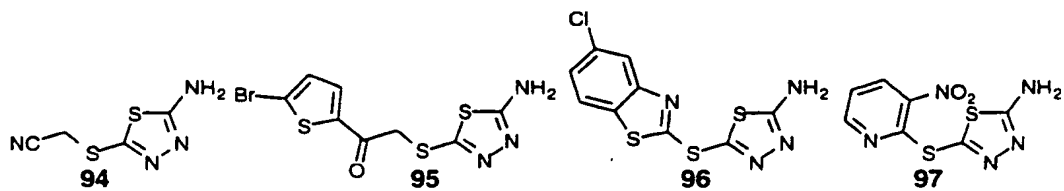
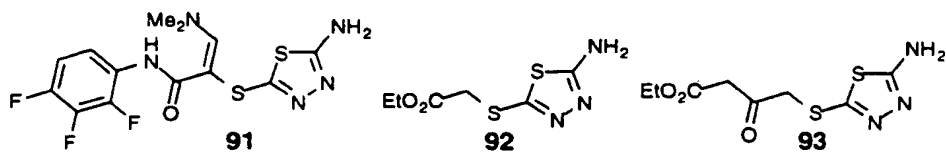
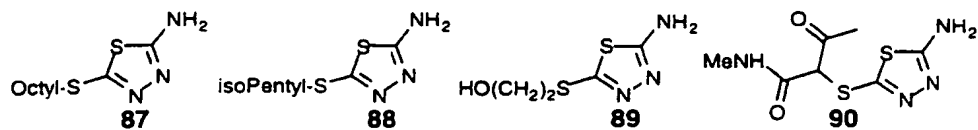
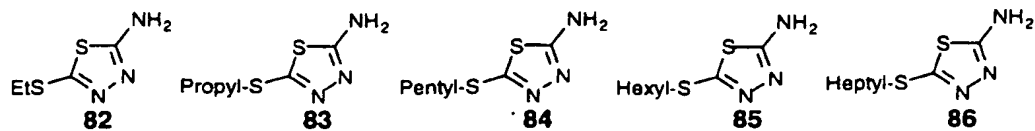
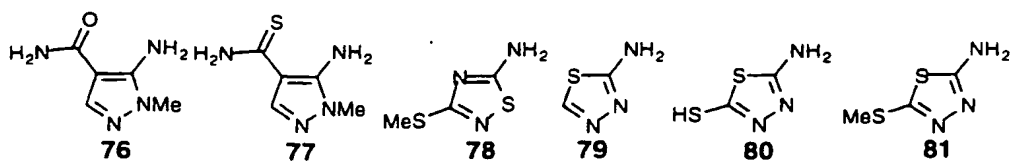


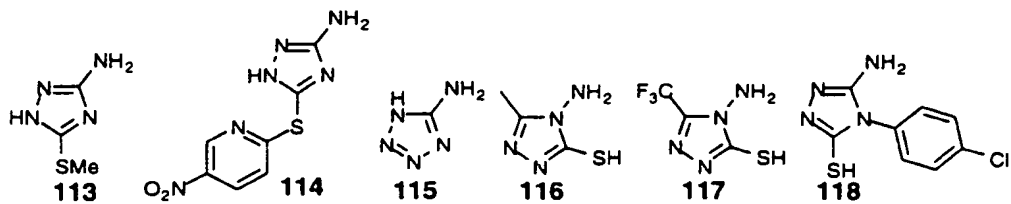
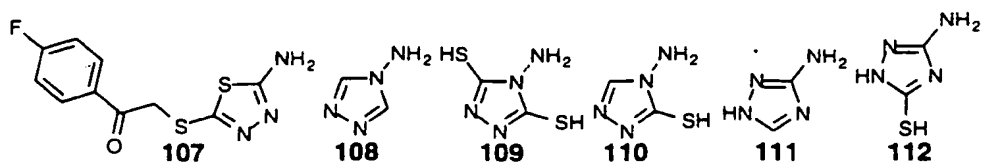
2600



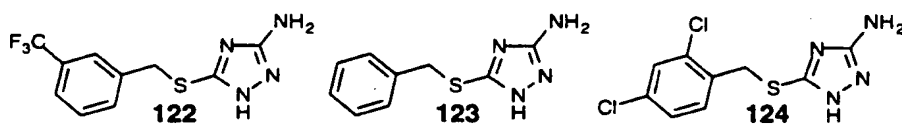
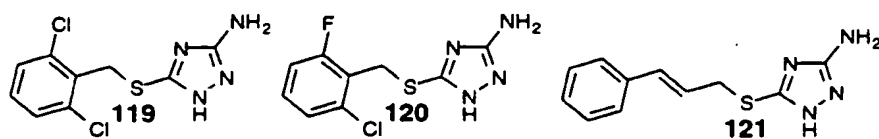
2610 Table 12. Amines of the type A-NH₂



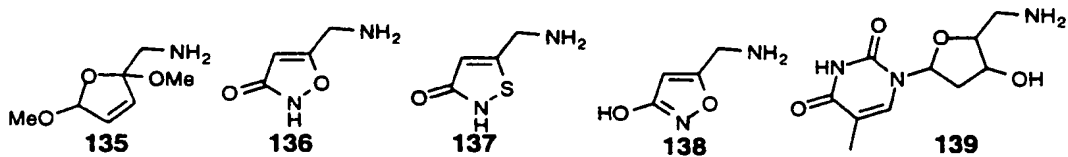
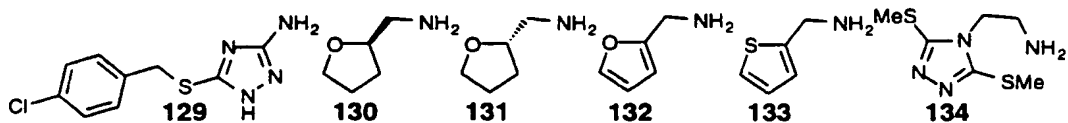
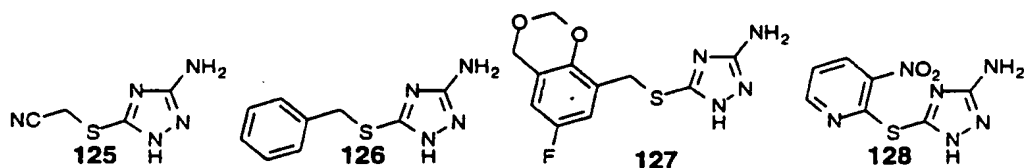




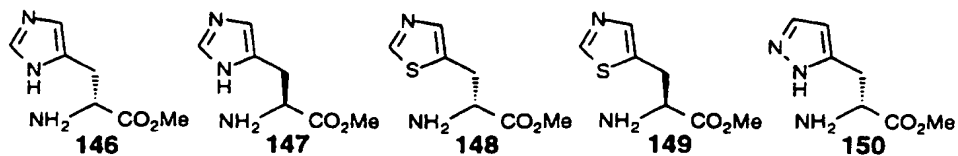
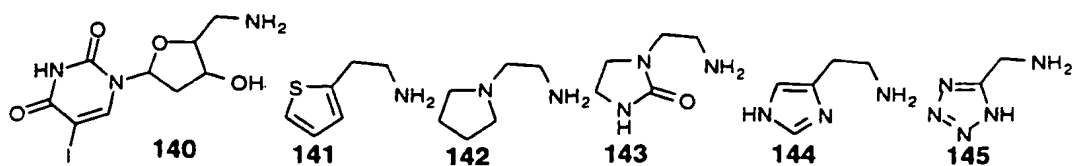
2655



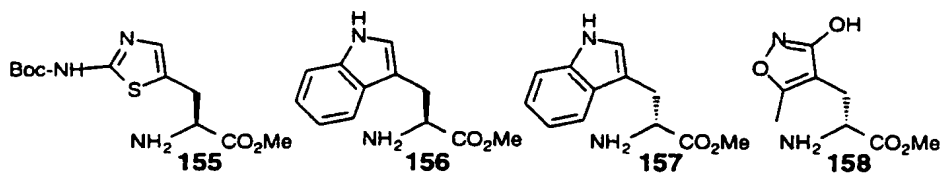
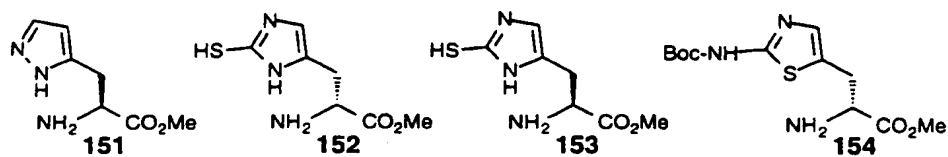
2660



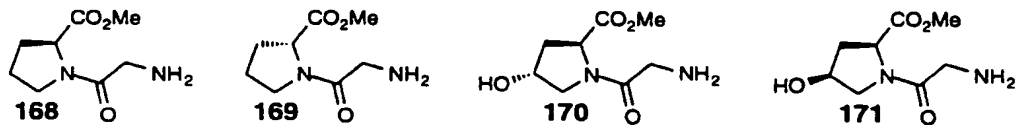
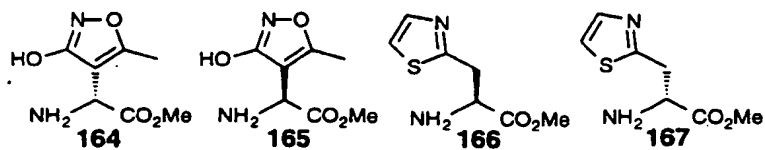
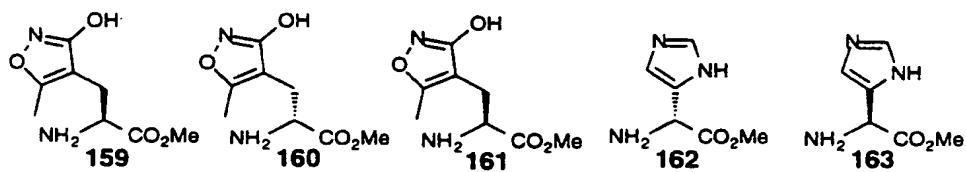
2665



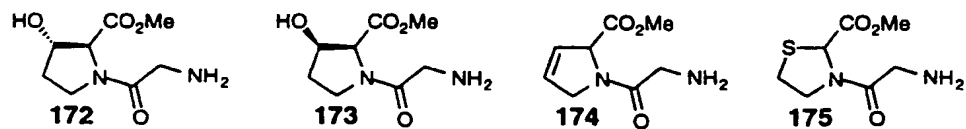
2670

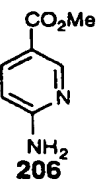
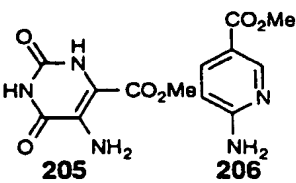
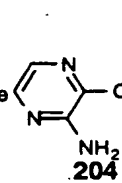
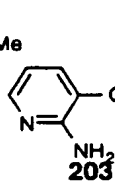
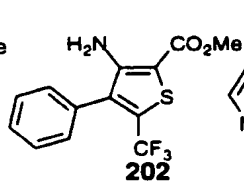
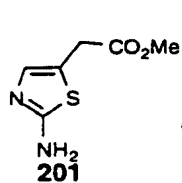
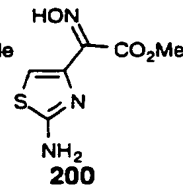
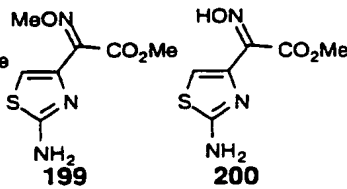
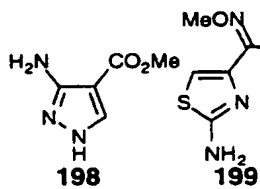
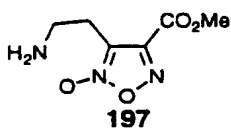
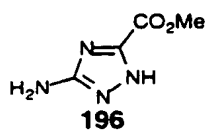
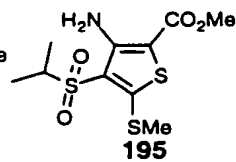
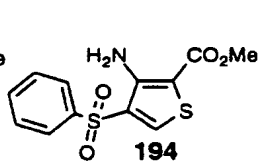
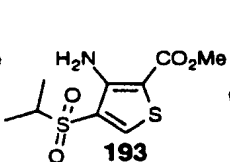
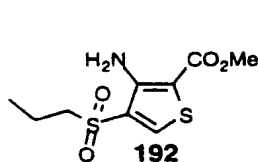
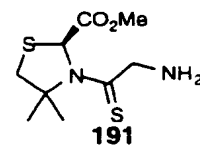
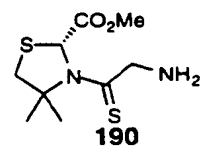
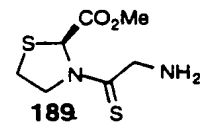
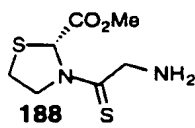
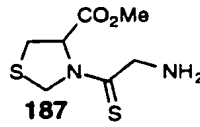
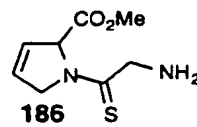
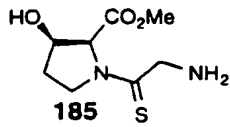
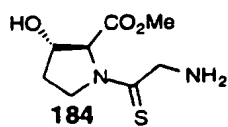
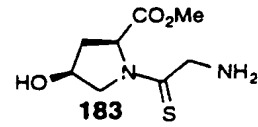
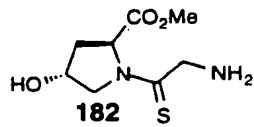
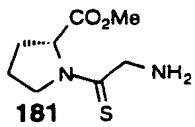
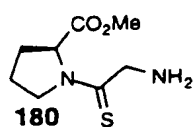
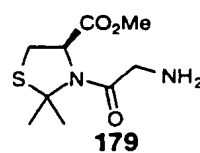
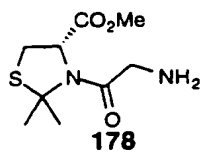
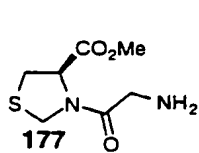
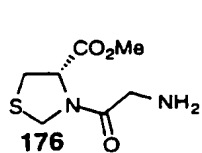


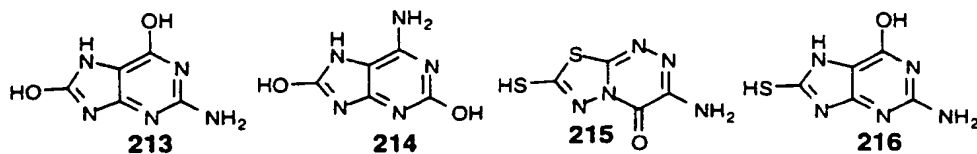
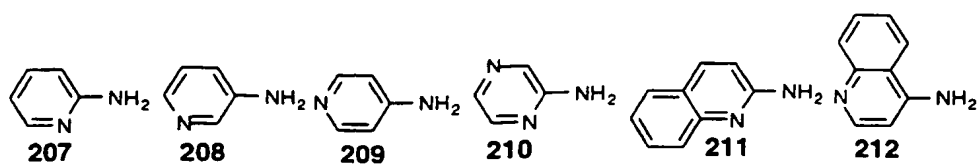
2675



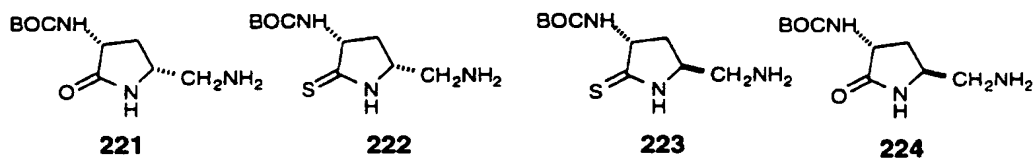
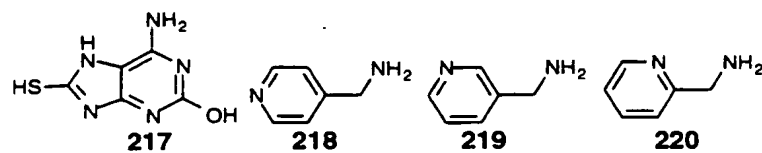
2680



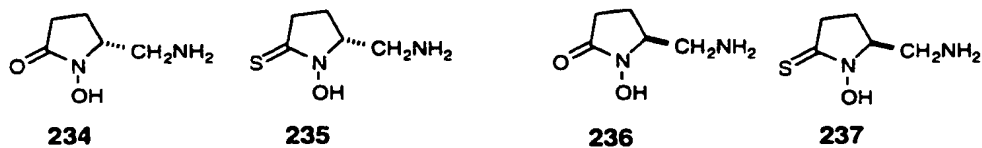
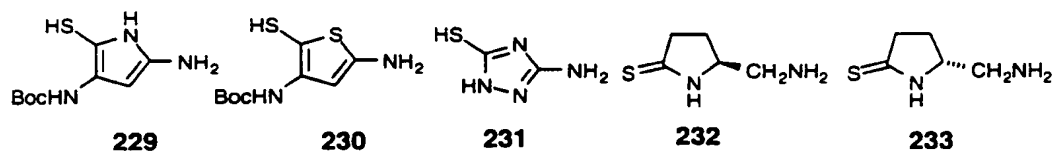
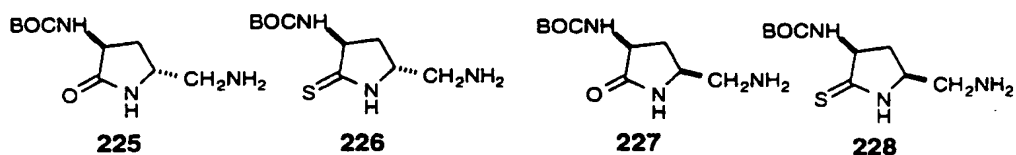




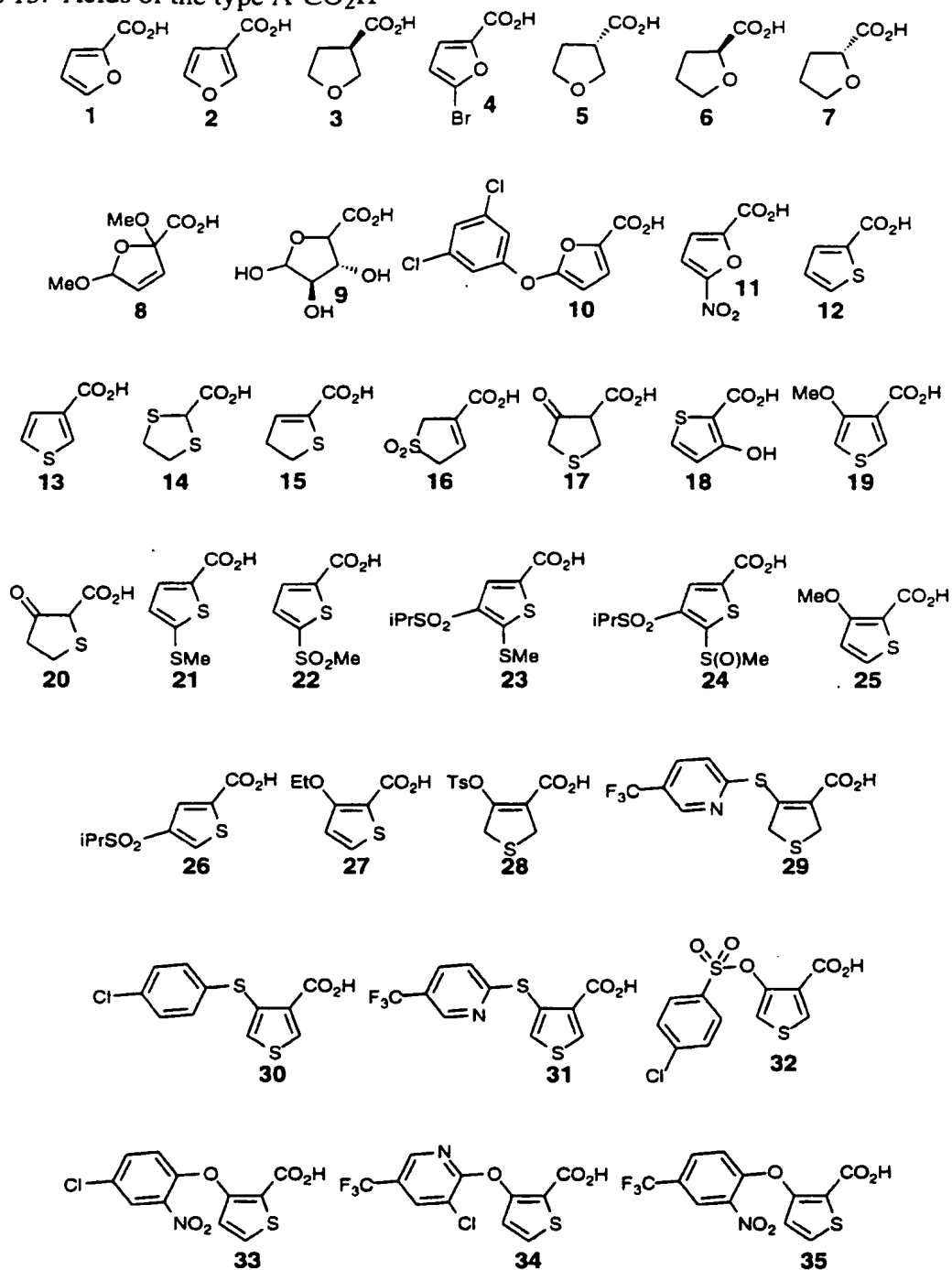
2700

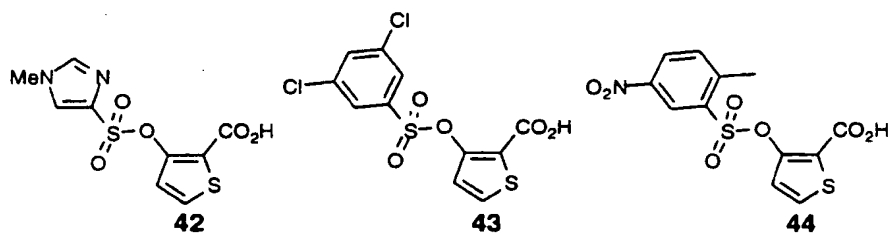
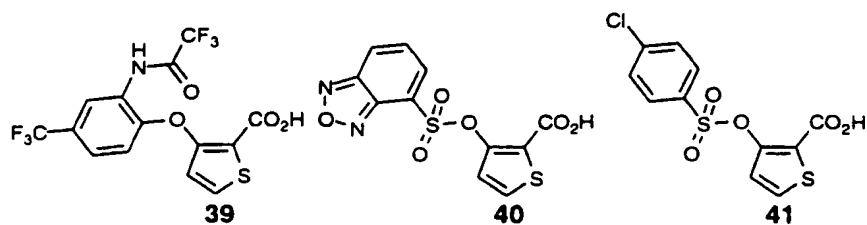
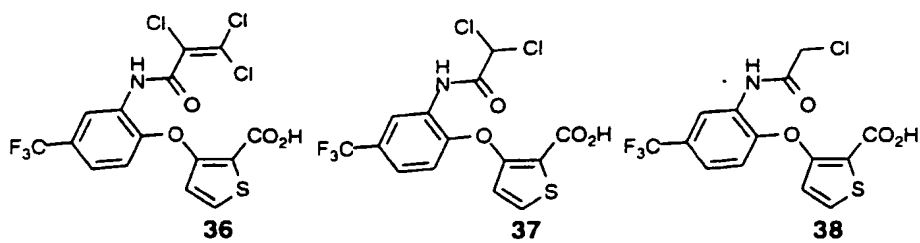


2705

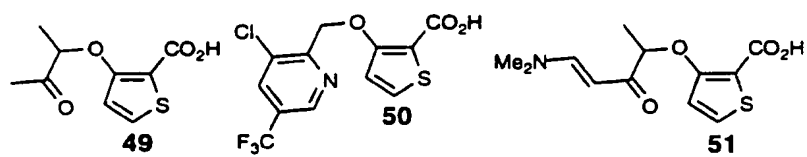
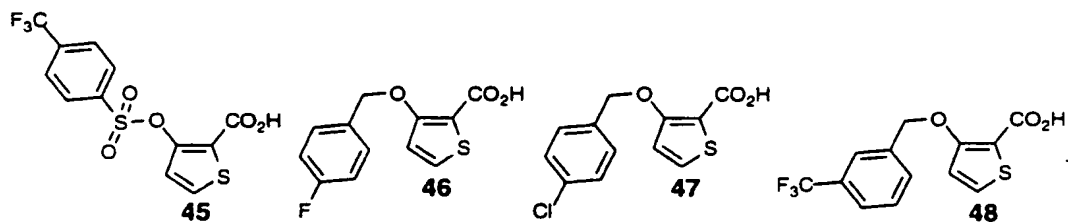


2710

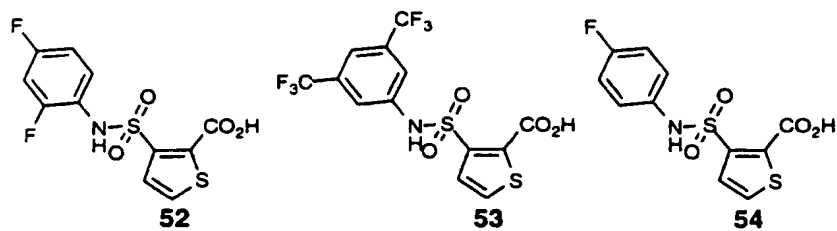
Table 13. Acids of the type A-CO₂H

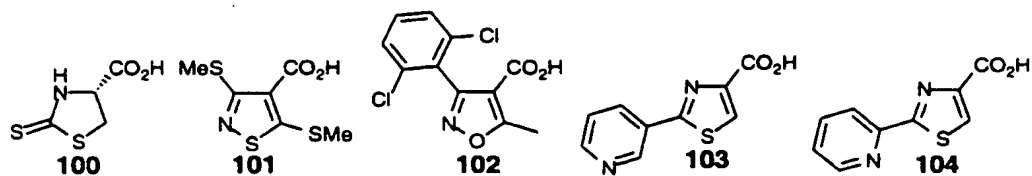
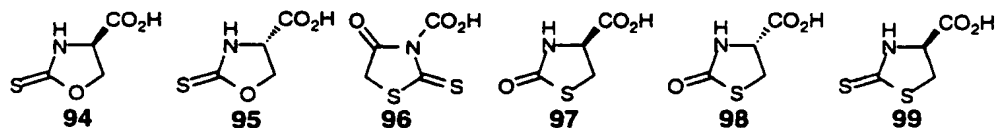
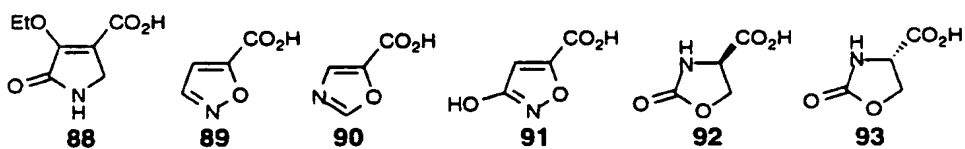
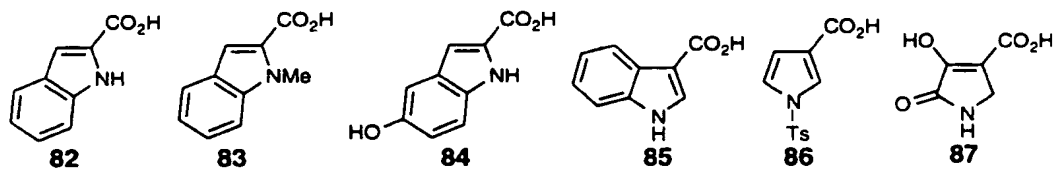
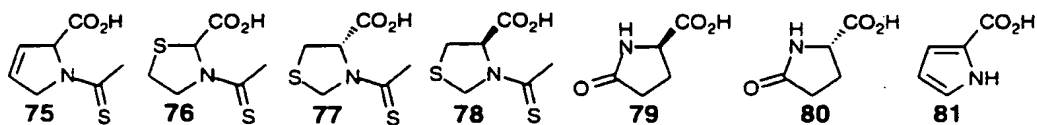
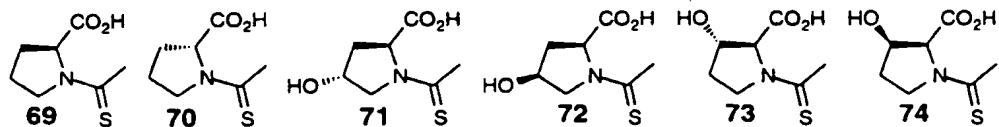
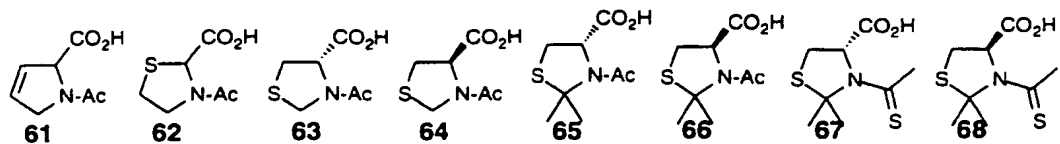
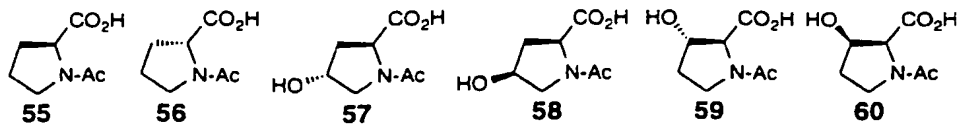


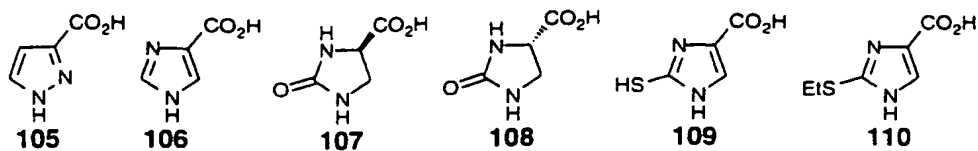
2730



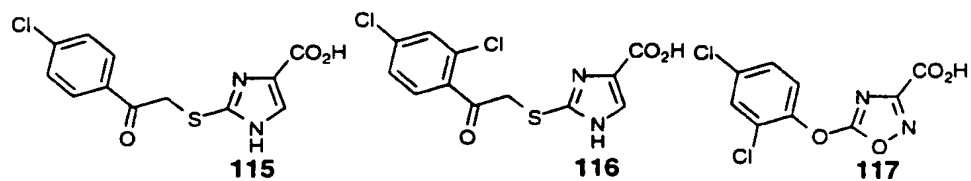
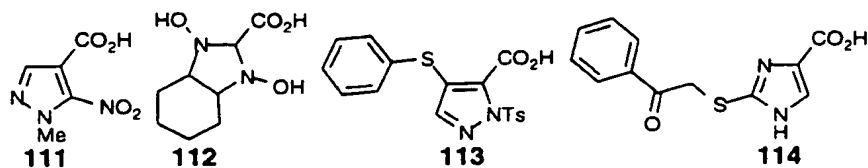
2735



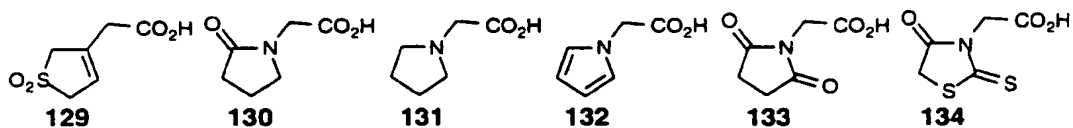
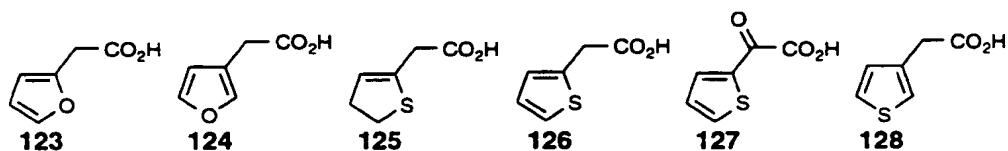
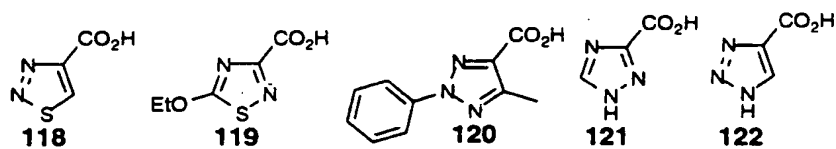




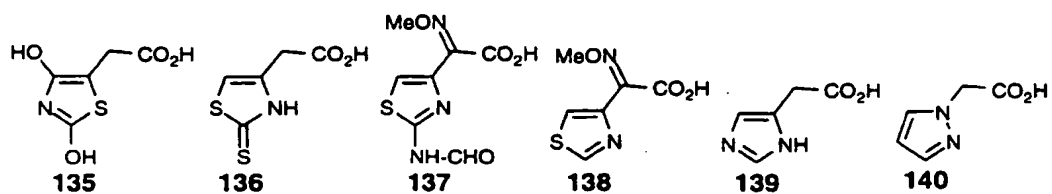
2755

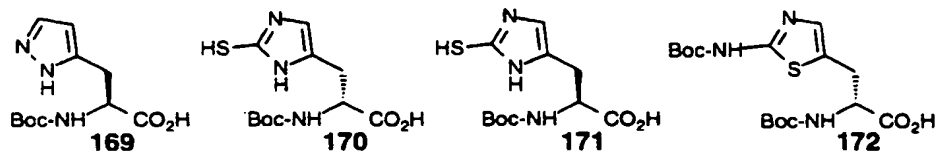
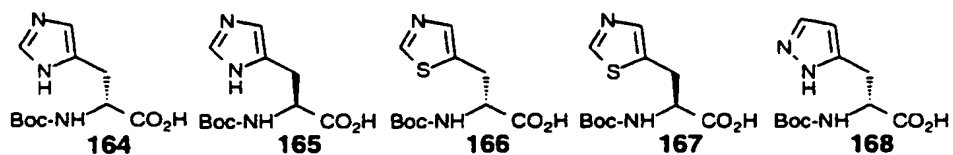
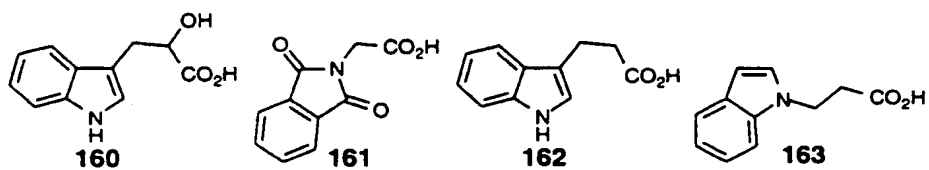
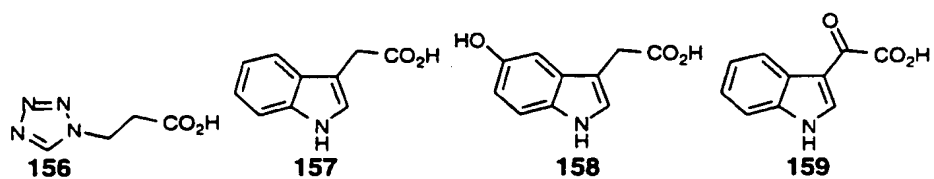
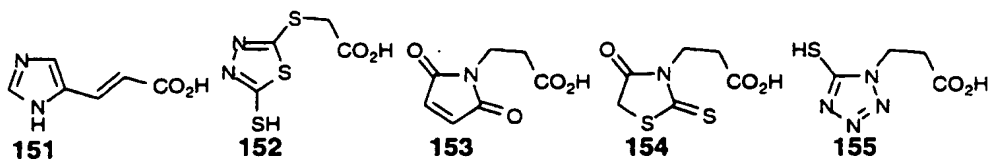
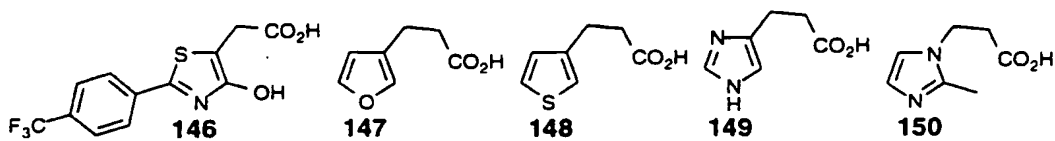
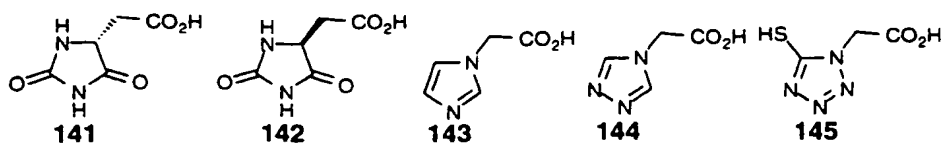


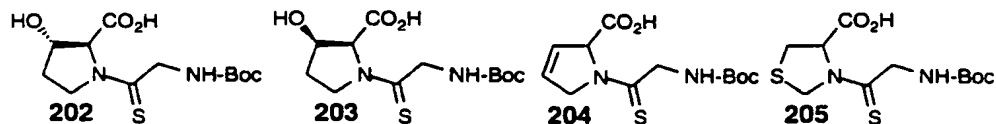
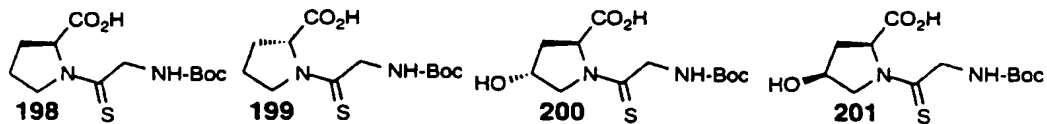
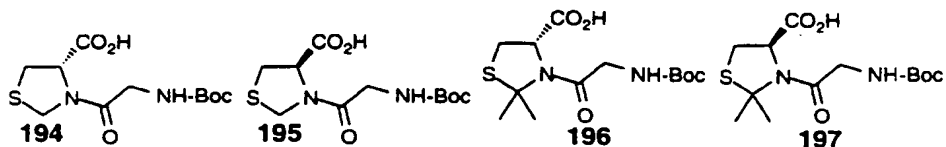
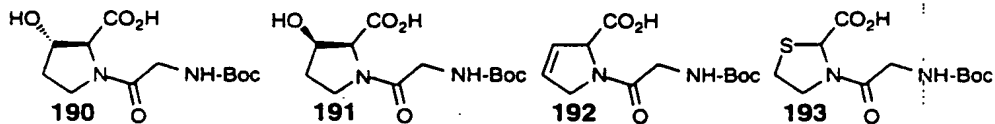
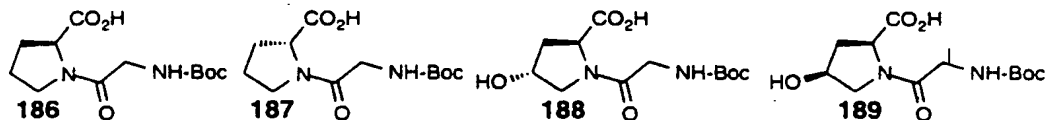
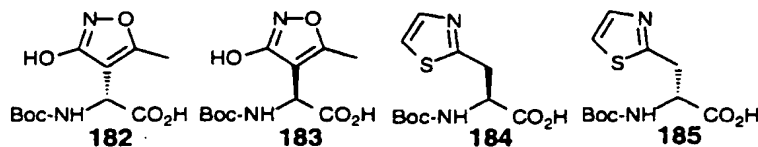
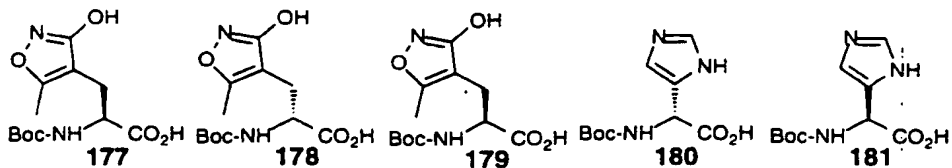
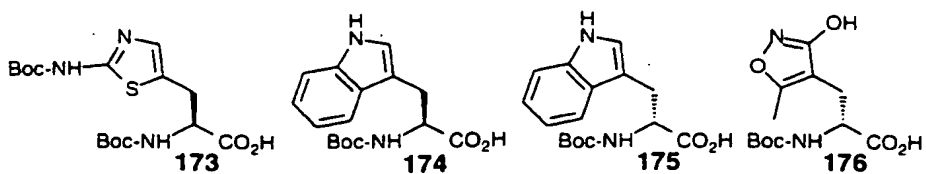
2760

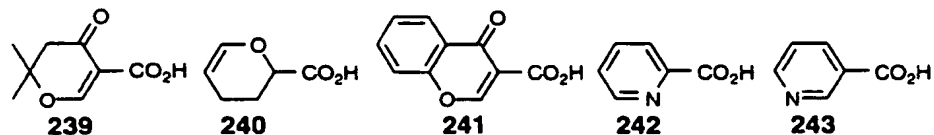
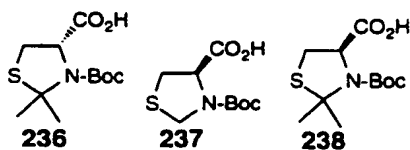
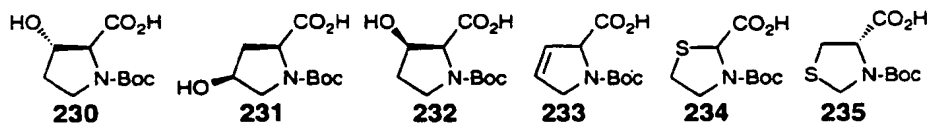
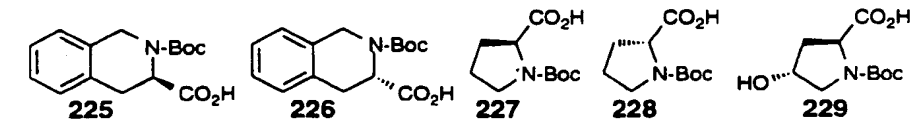
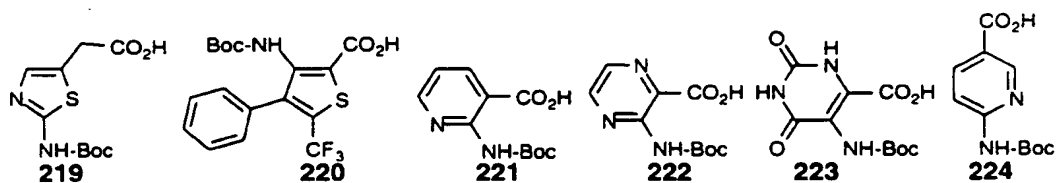
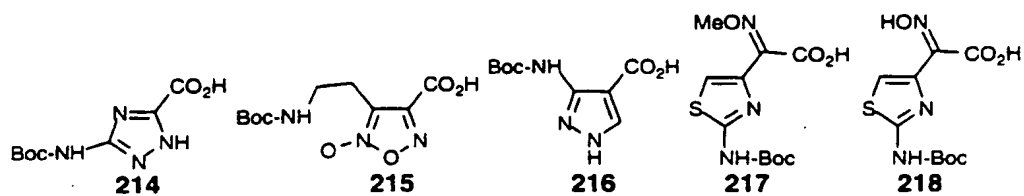
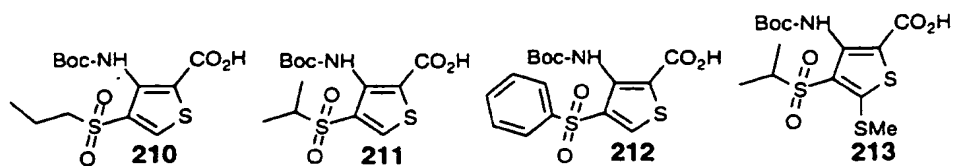
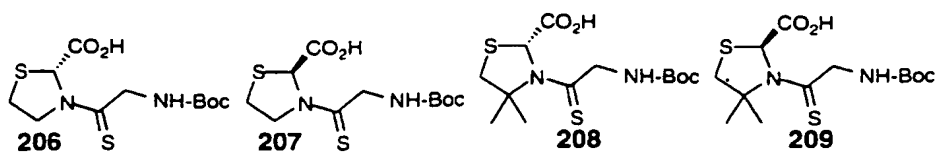


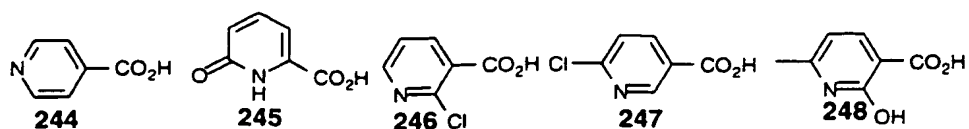
2765



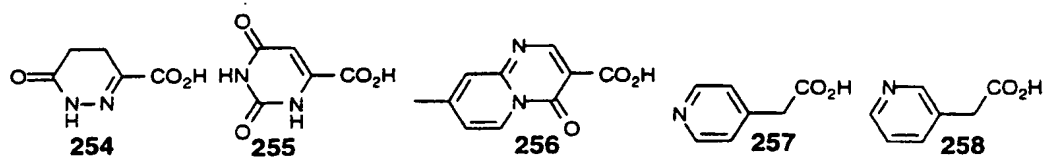
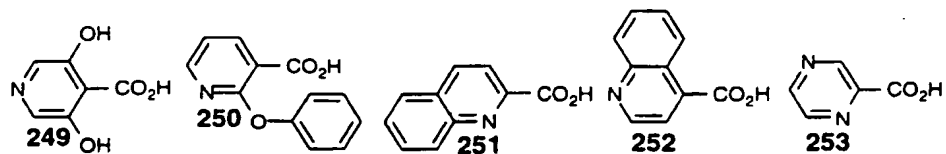




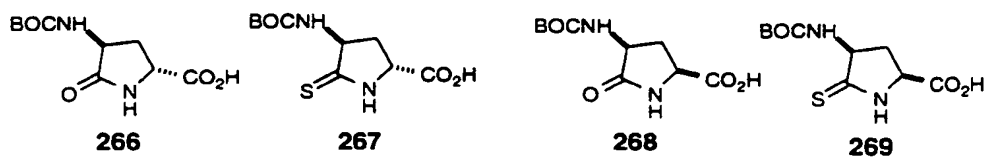
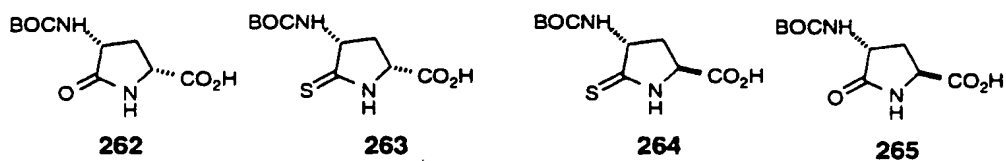
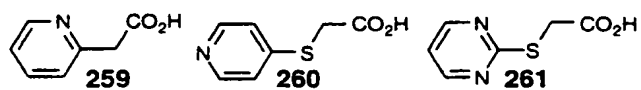




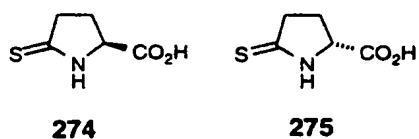
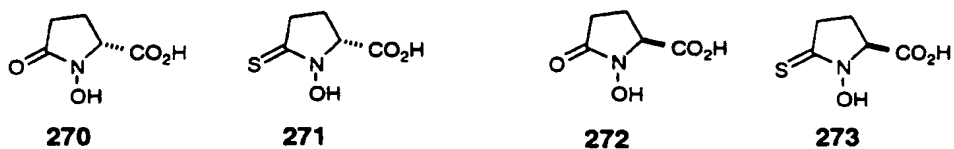
2815



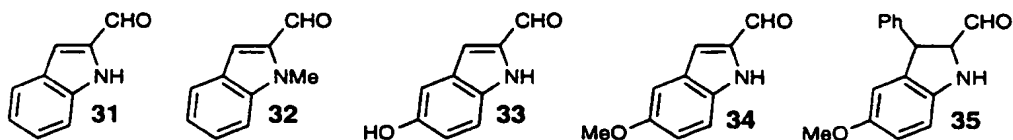
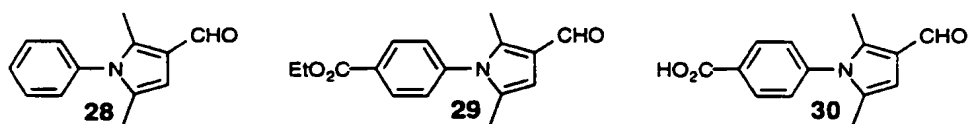
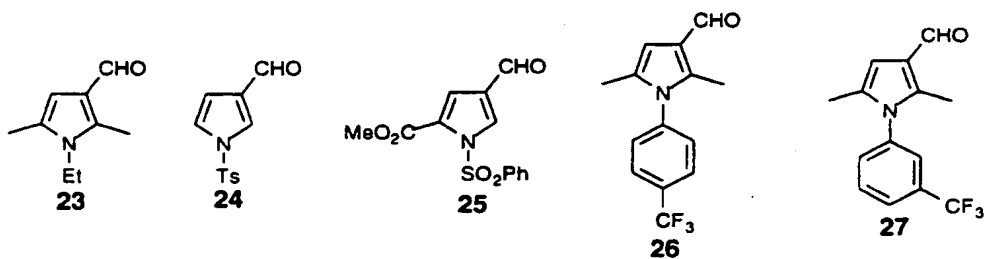
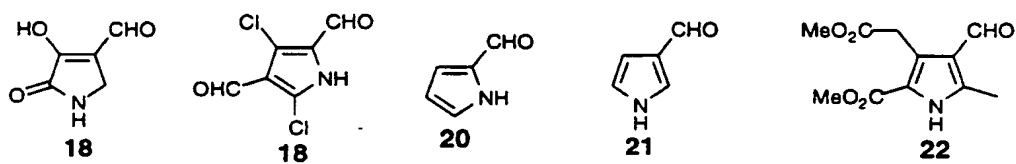
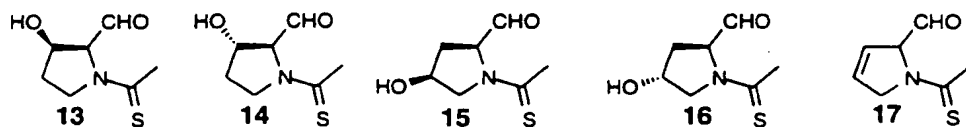
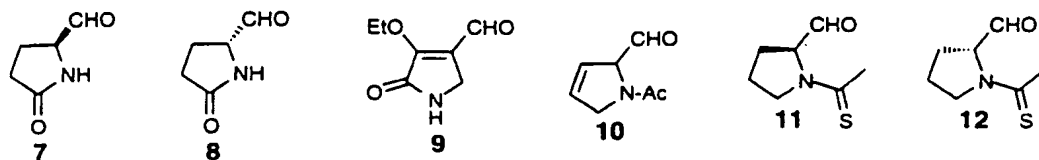
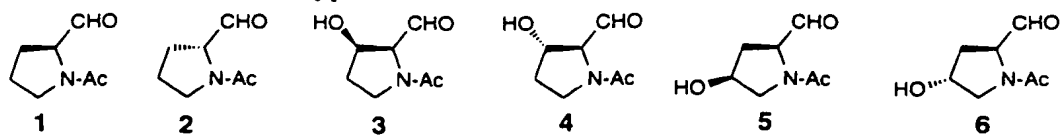
2820



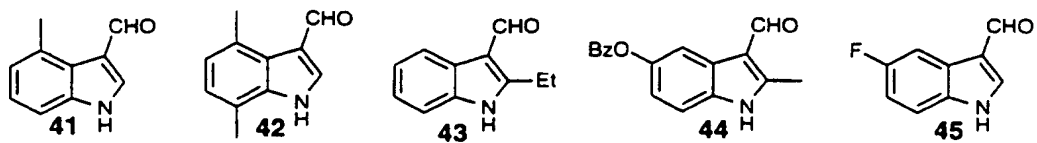
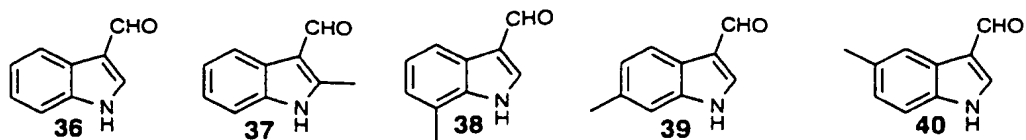
2825



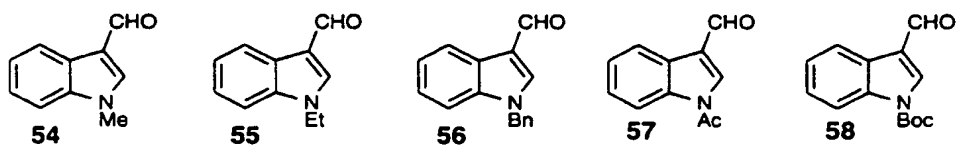
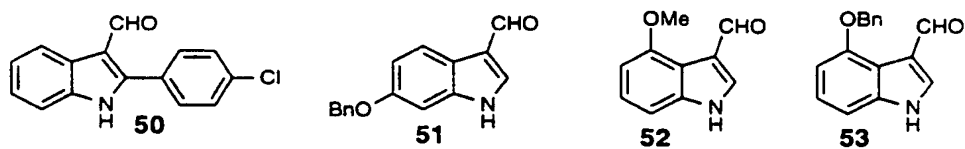
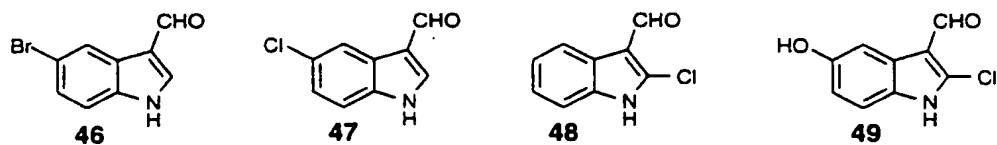
2830 Table 14. Aldehydes of the type A-CHO



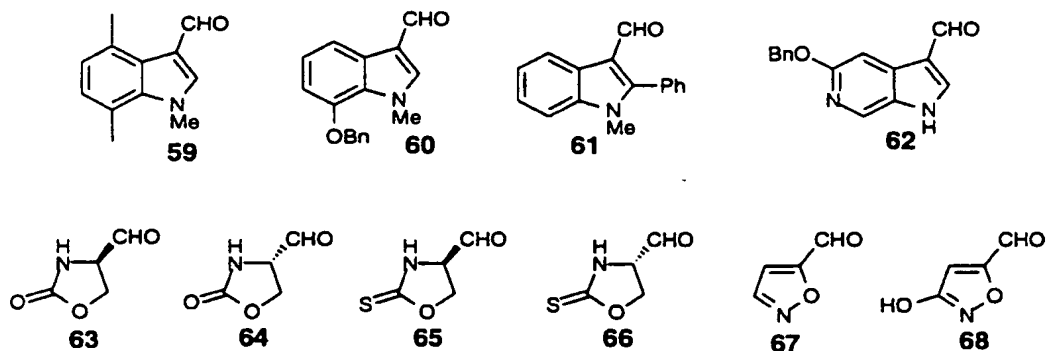
2845

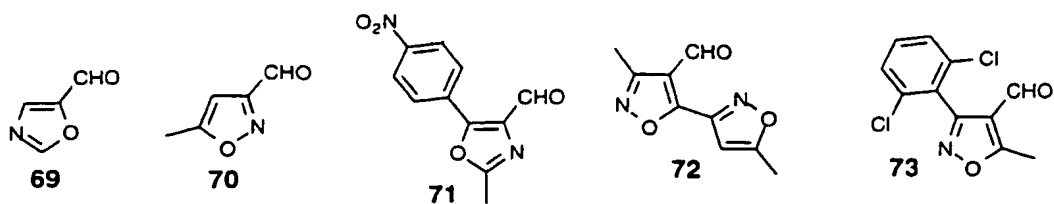


2850

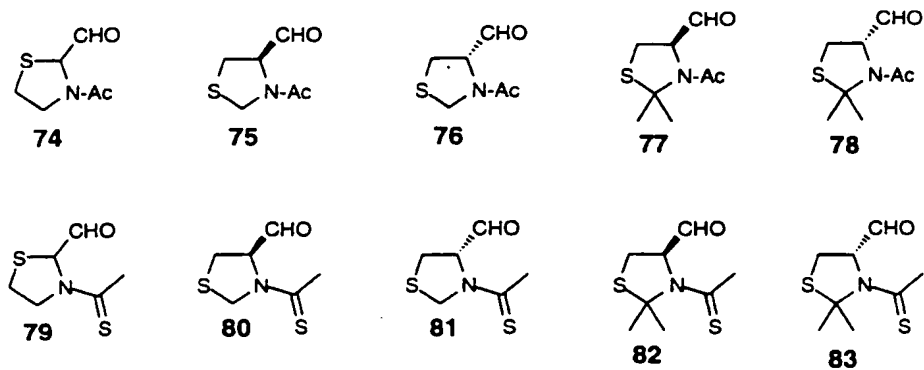


2855

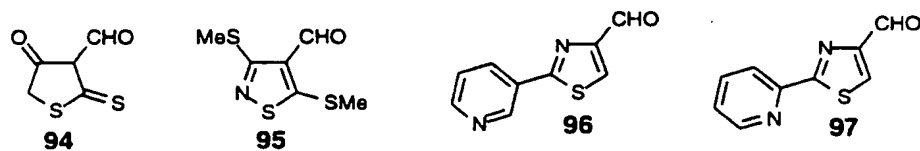
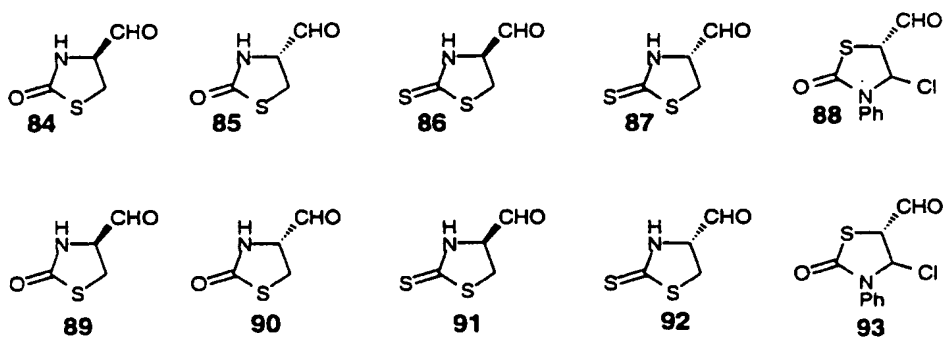




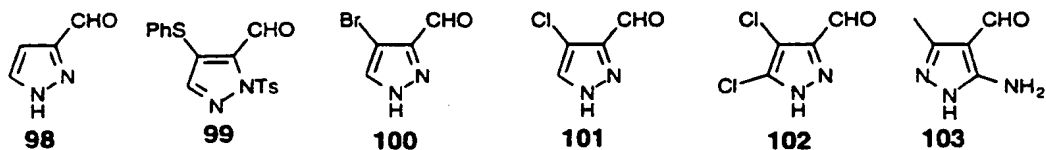
2860

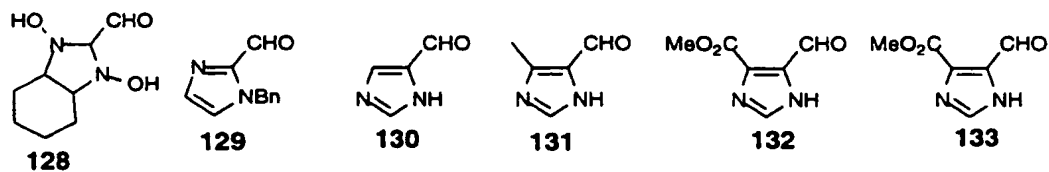
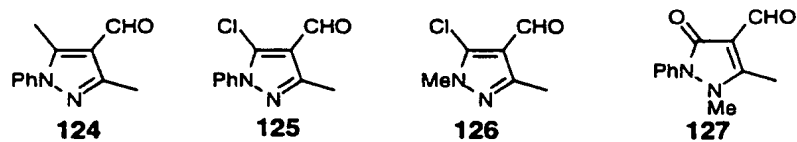
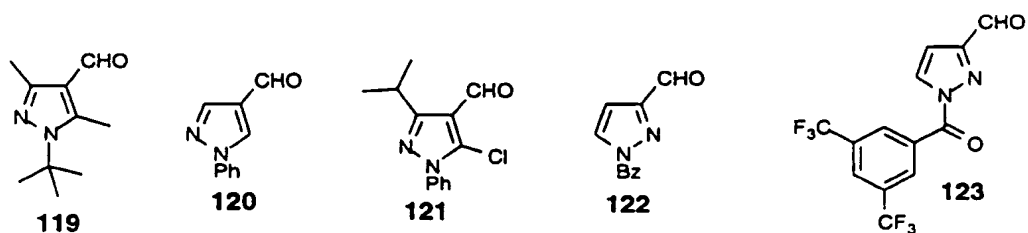
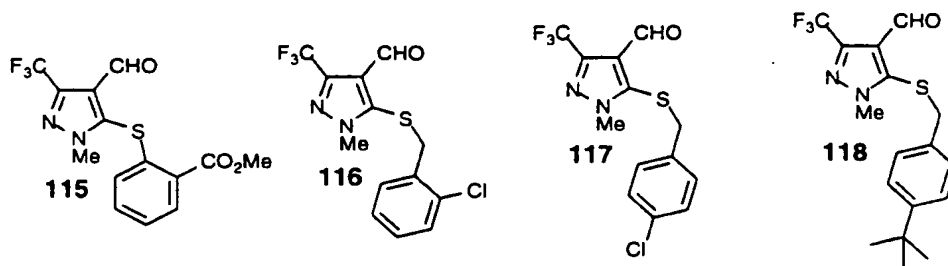
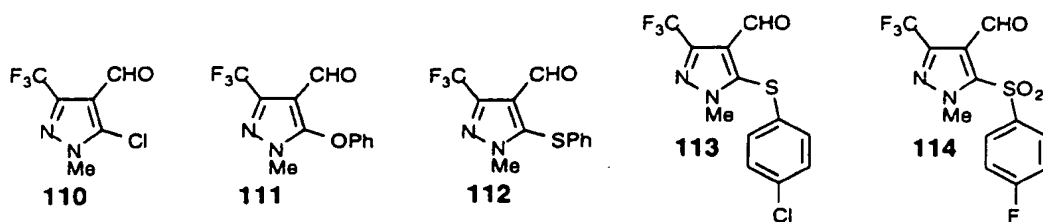
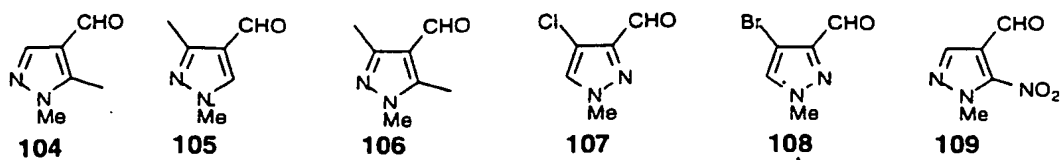


2865

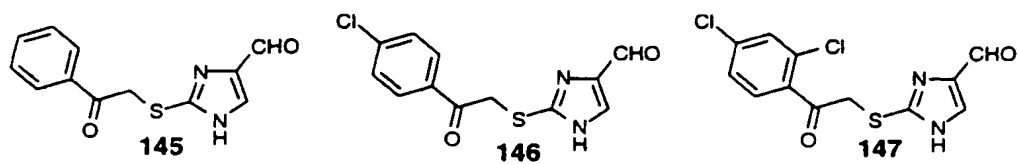
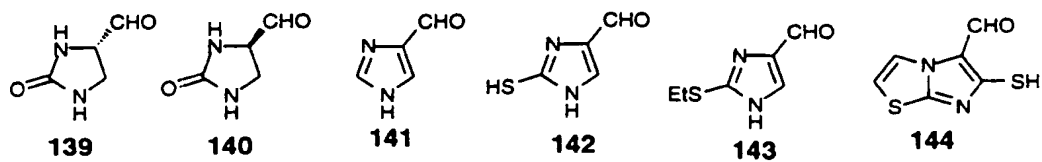
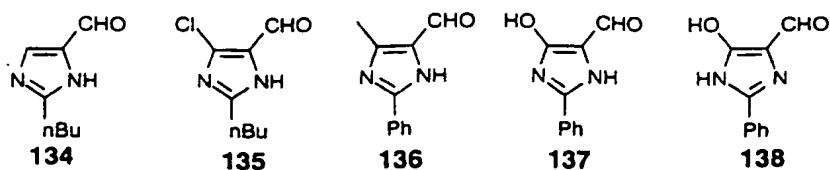


2870

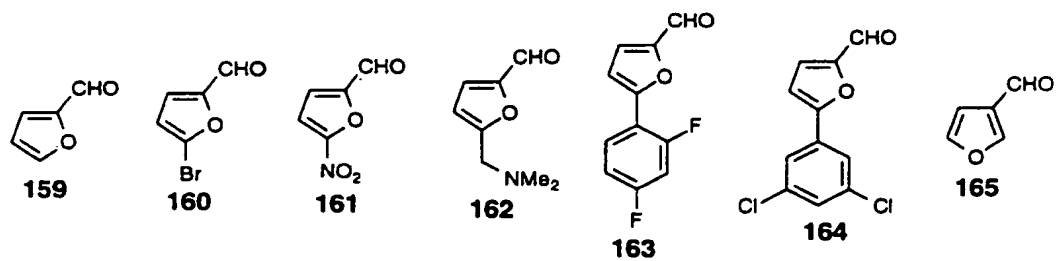
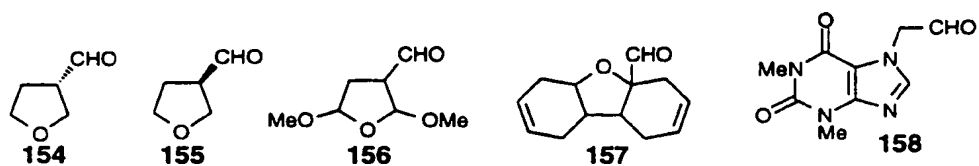
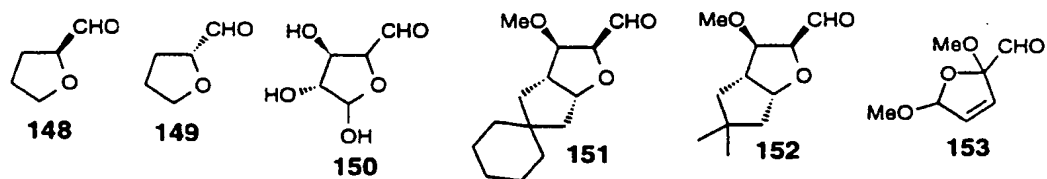




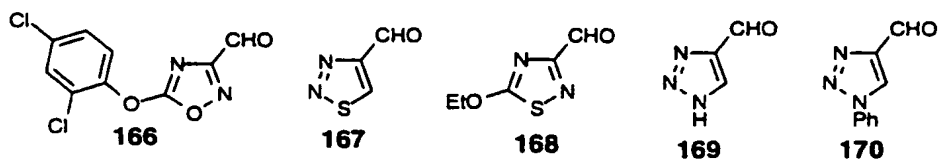
2885

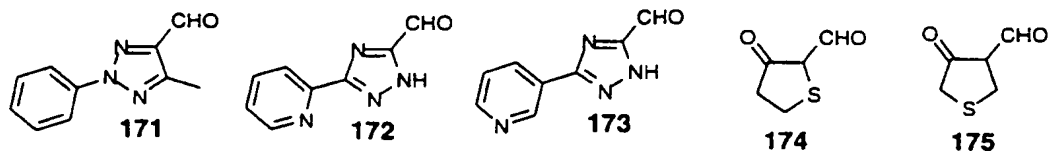


2890

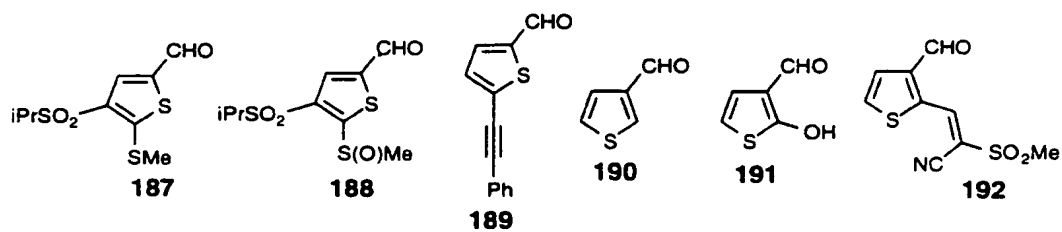
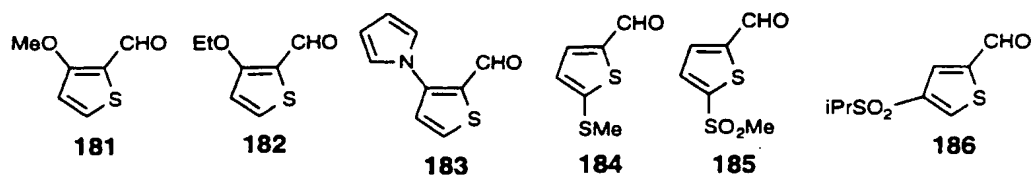
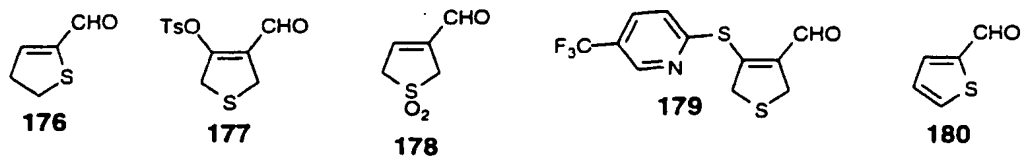


2895

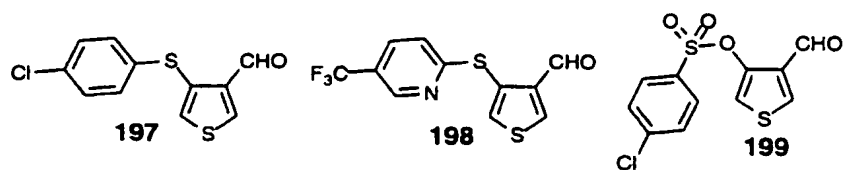
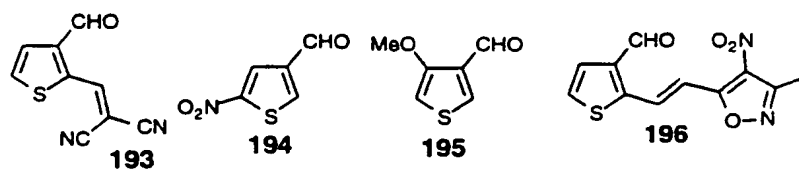




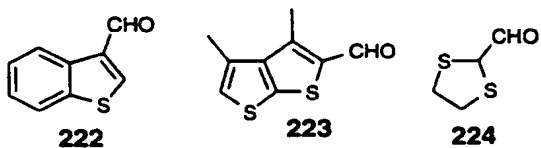
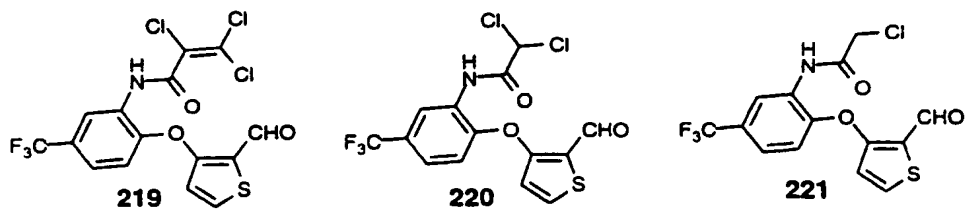
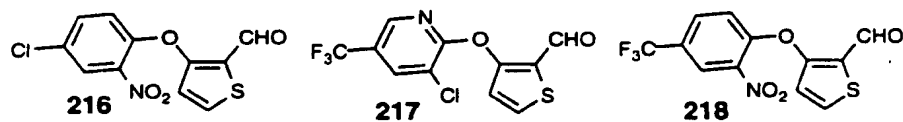
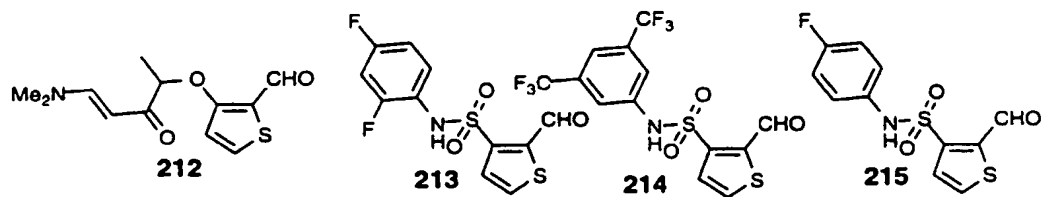
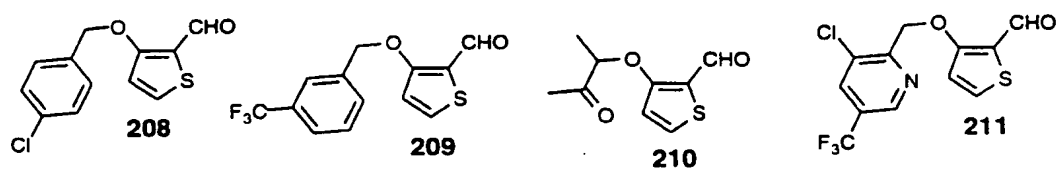
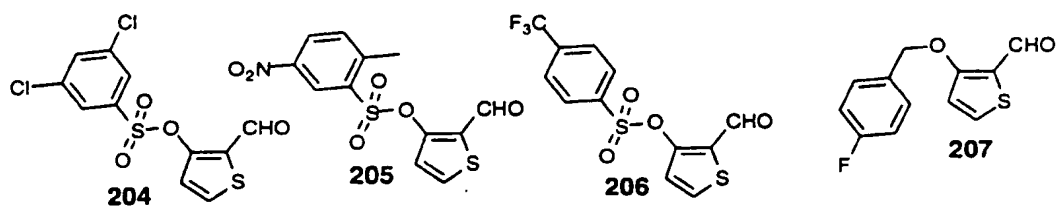
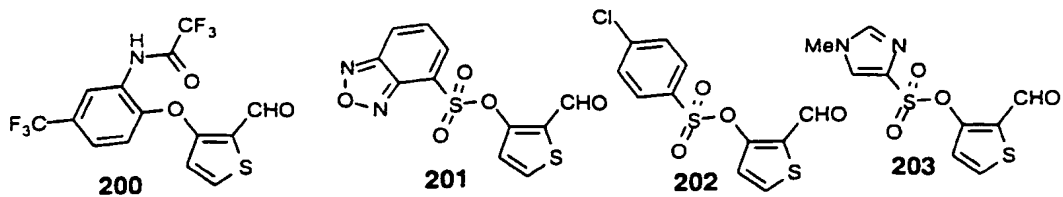
2900

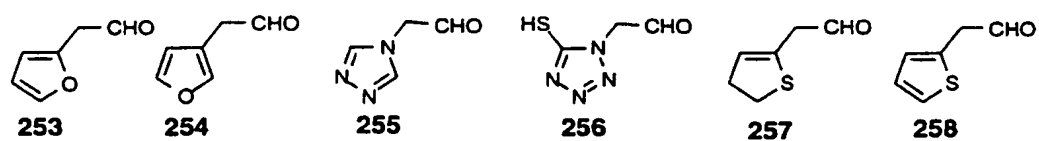
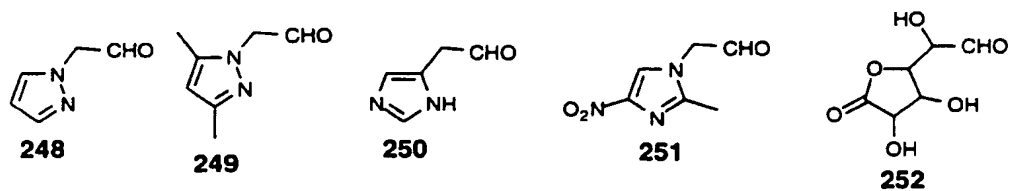
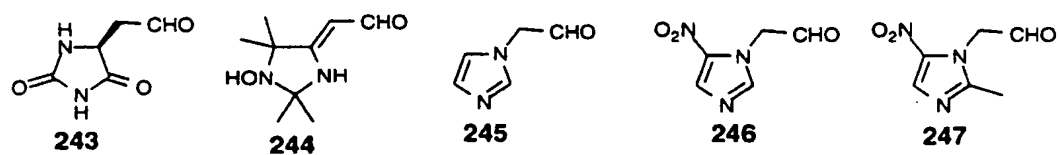
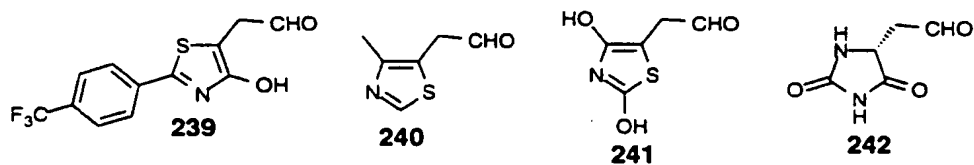
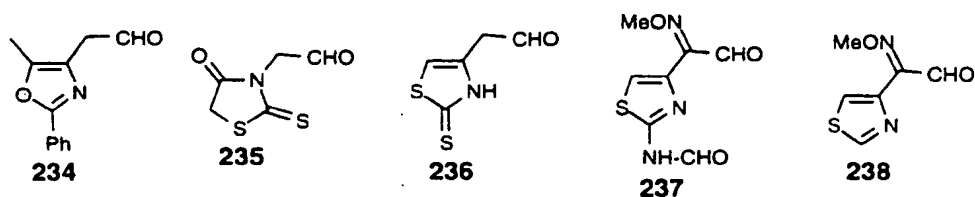
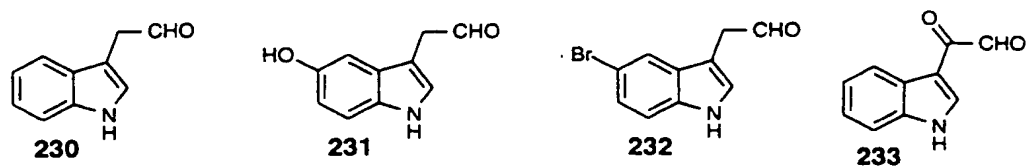
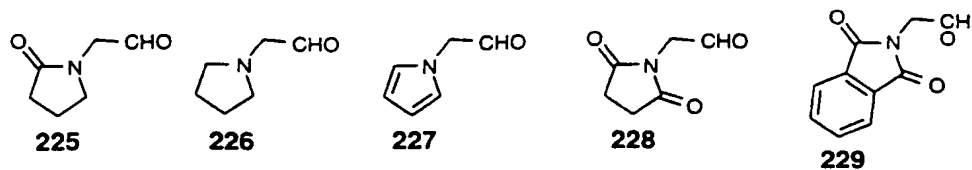


2905

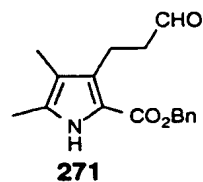
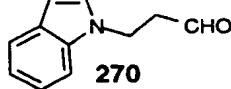
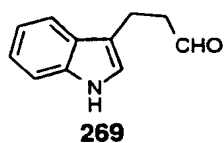
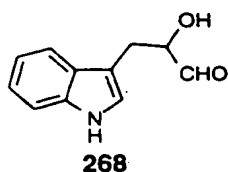
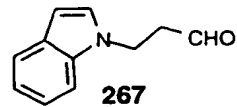
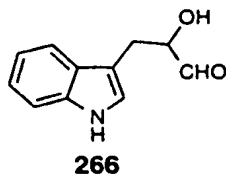
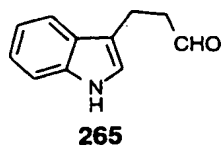
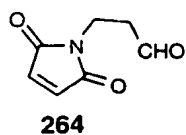
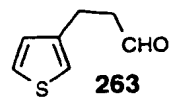
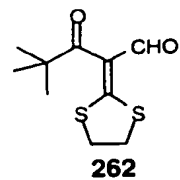
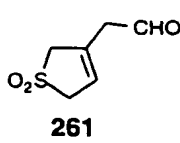
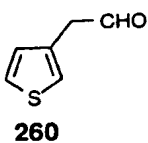
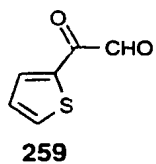


2910

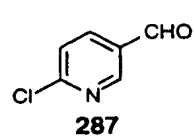
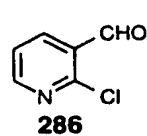
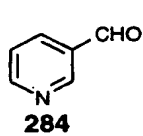
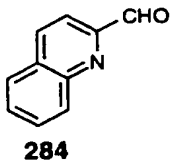
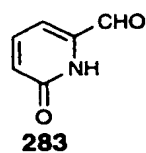
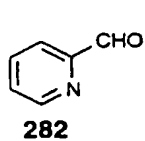
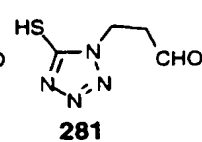
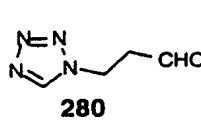
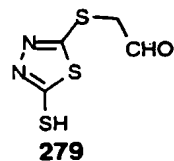
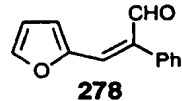
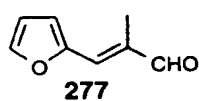
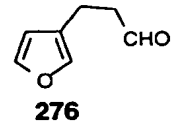
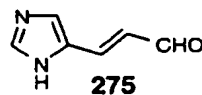
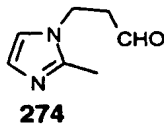
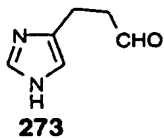
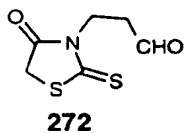




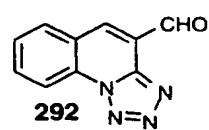
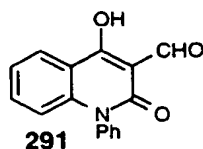
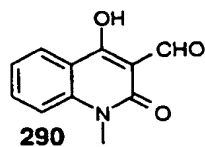
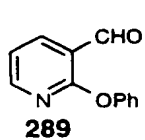
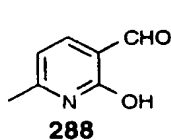
2940

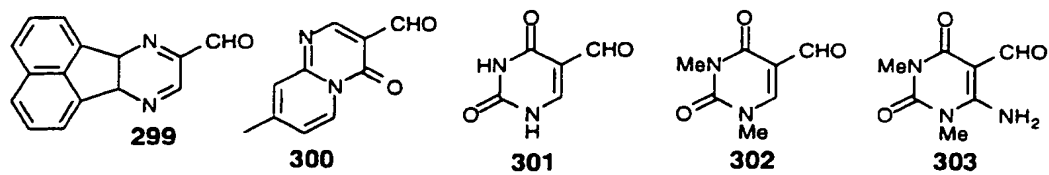
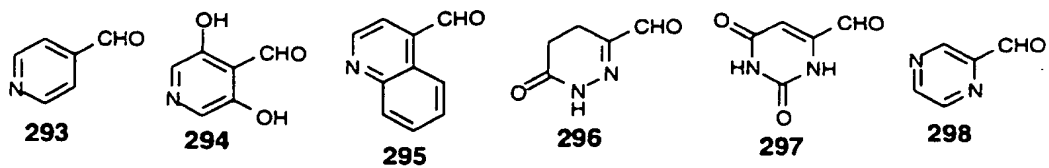


2945

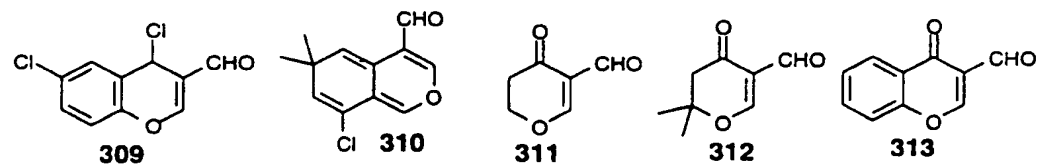
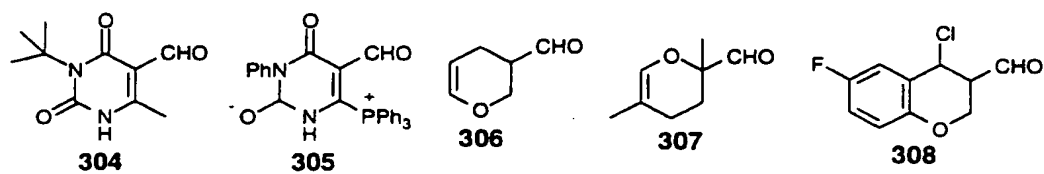


2950

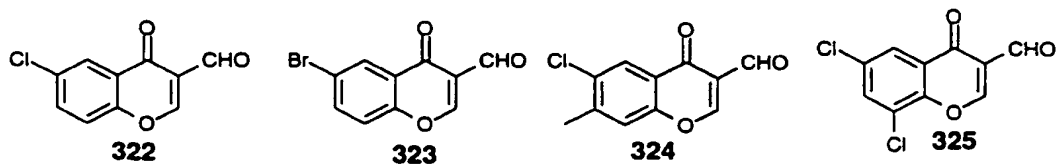
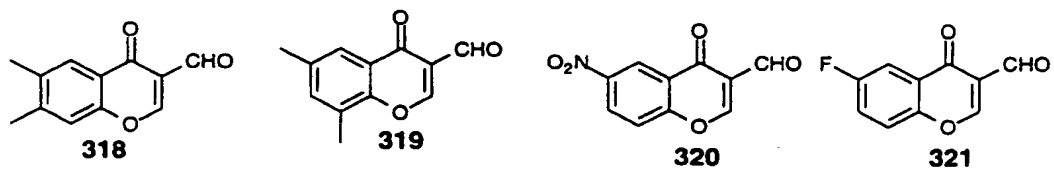
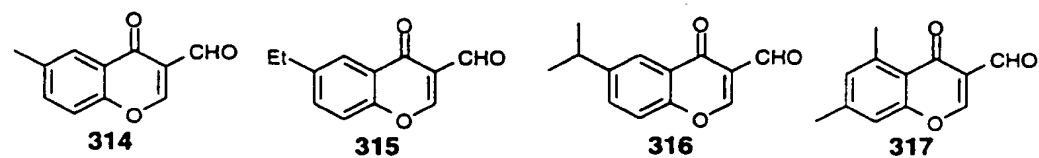




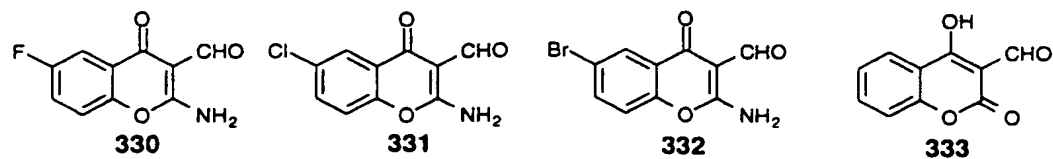
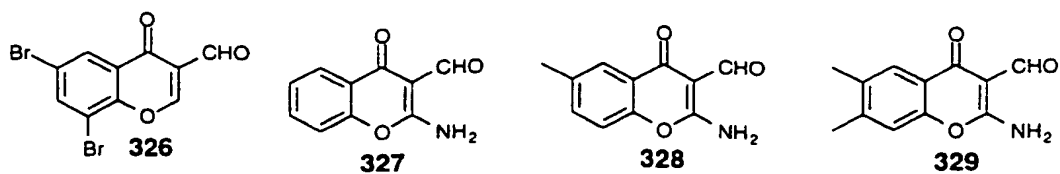
2955



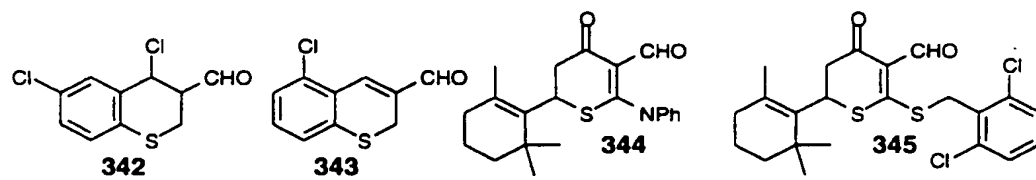
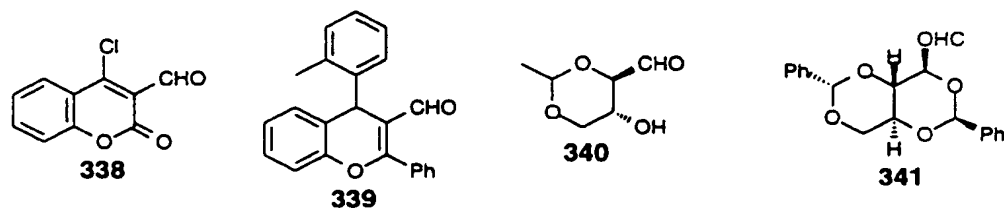
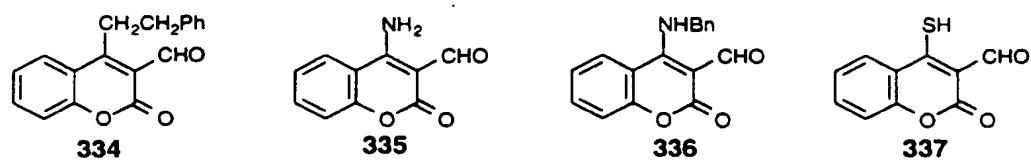
2960



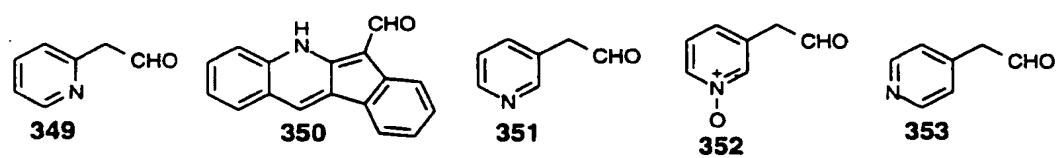
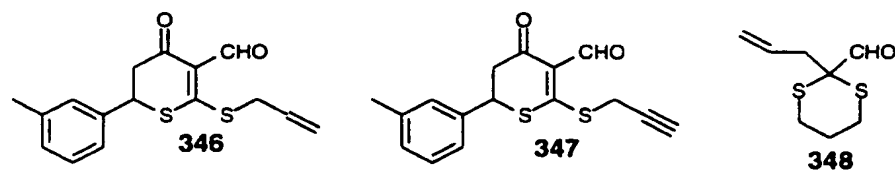
2965



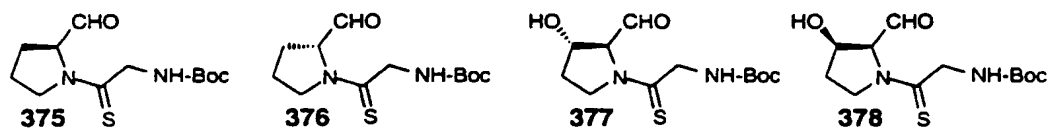
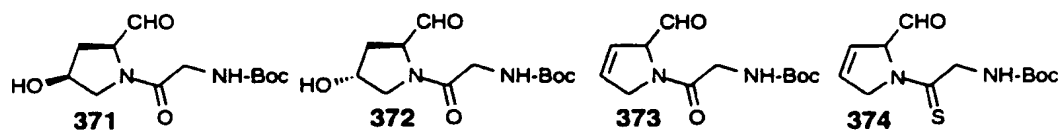
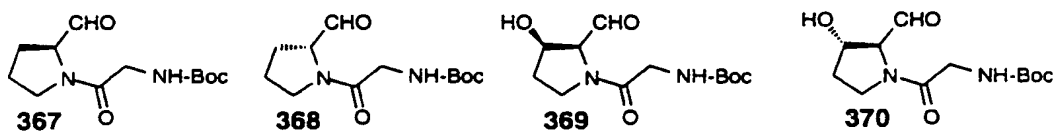
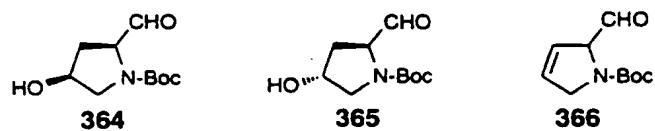
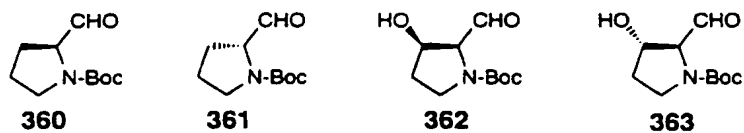
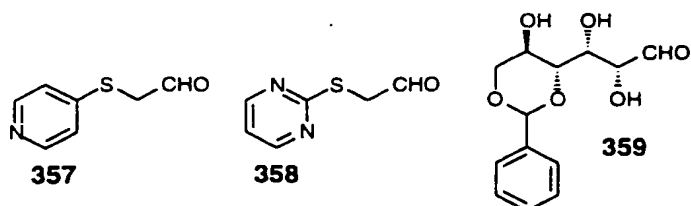
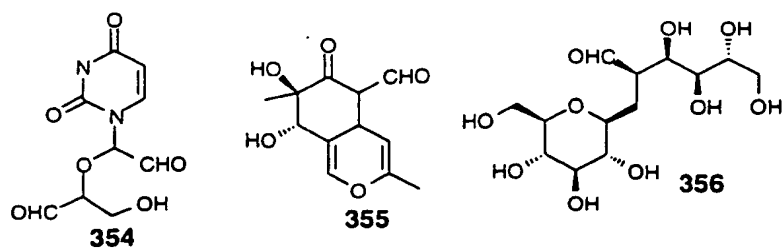
2970

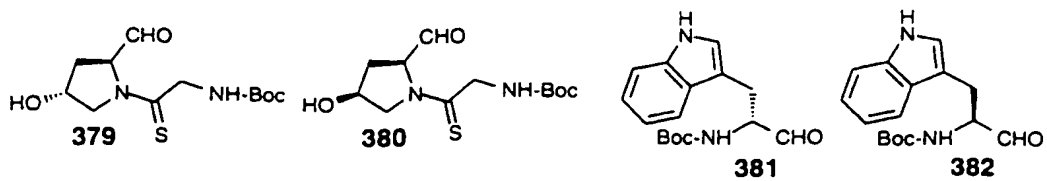


2975

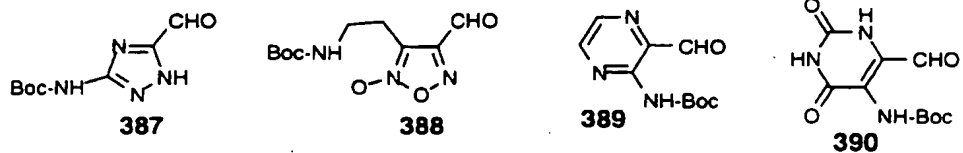
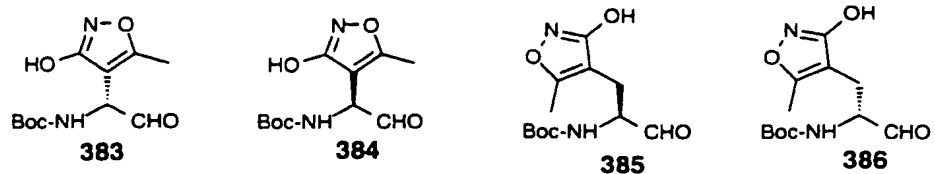


2980

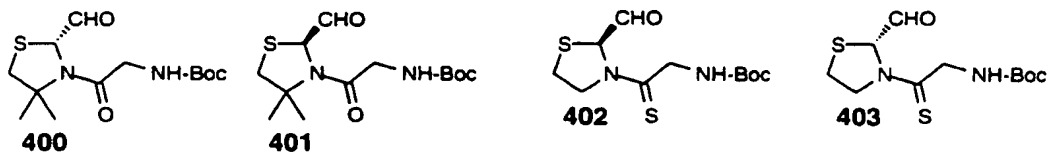
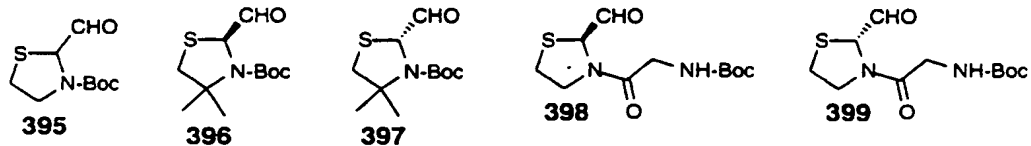
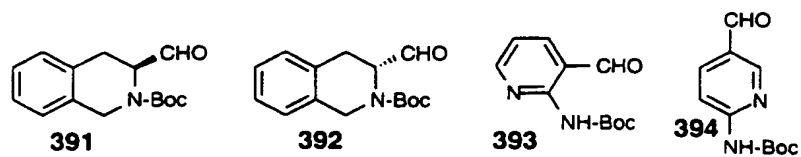




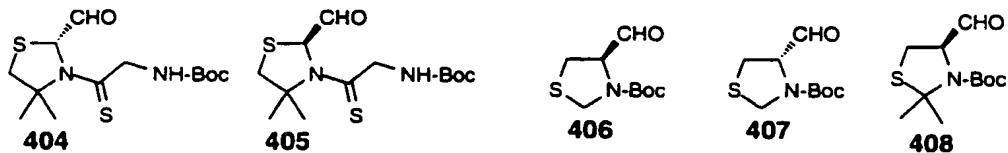
2995

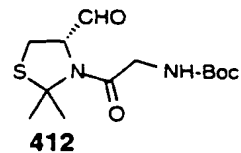
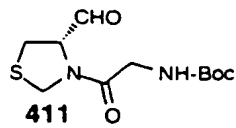
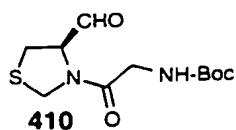
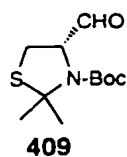


3000

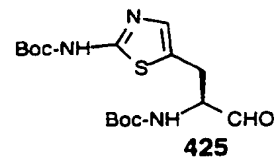
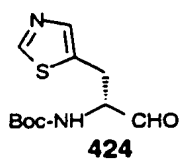
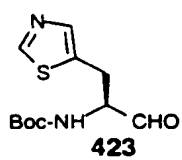
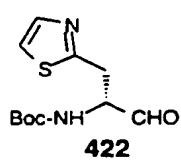
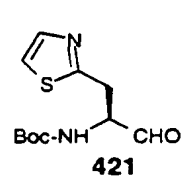
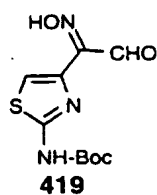
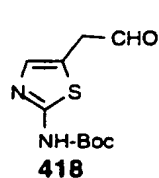
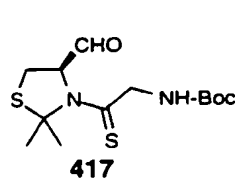
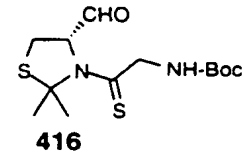
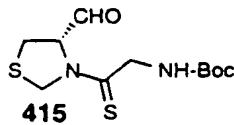
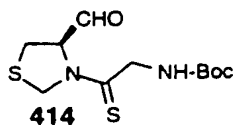
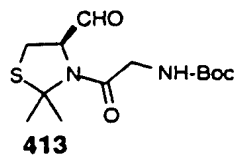


3005

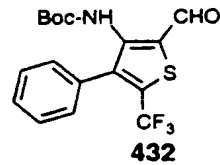
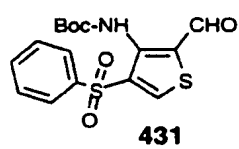
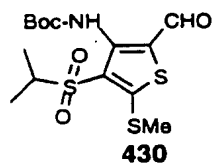
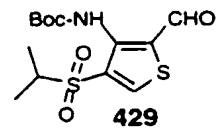
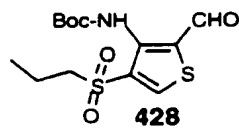
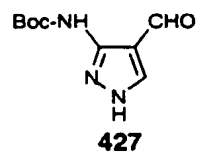
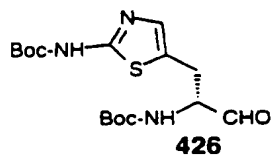




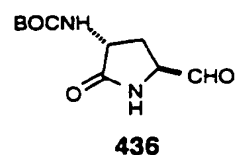
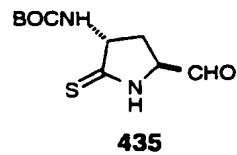
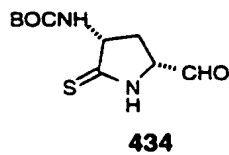
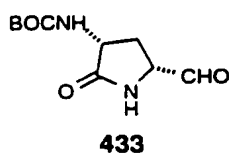
3010

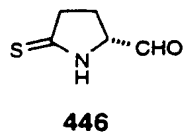
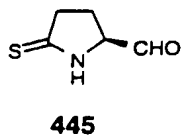
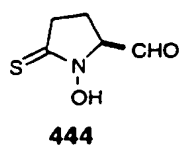
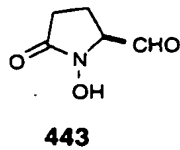
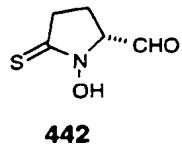
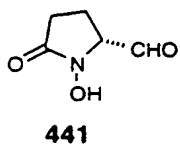
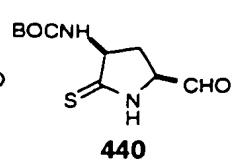
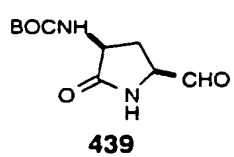
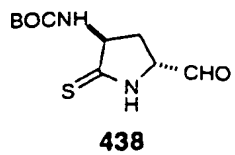
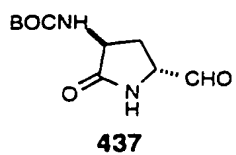


3015



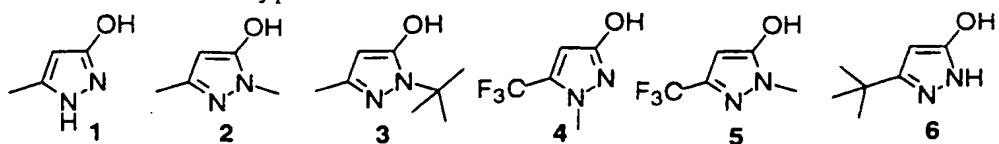
3020



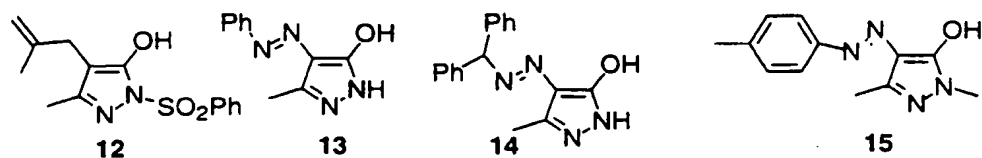
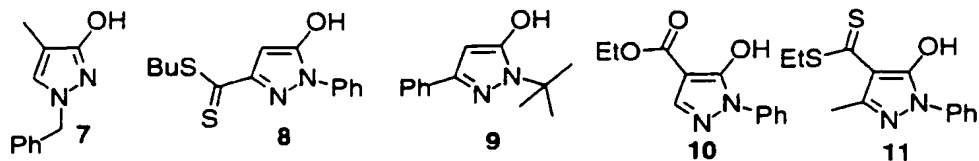


3025

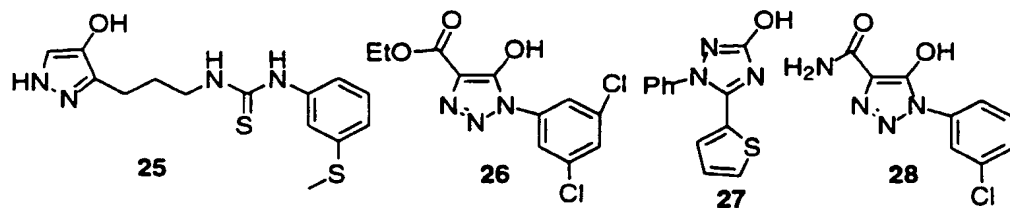
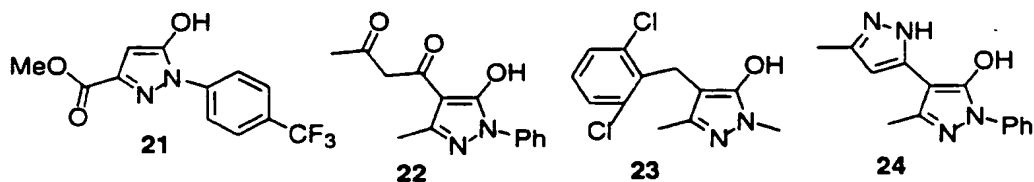
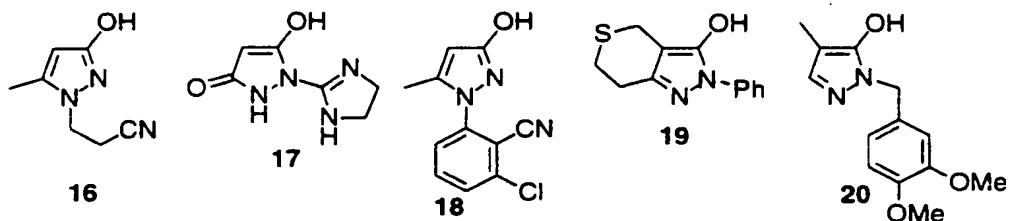
Table 15. Alcohols of the type A-OH



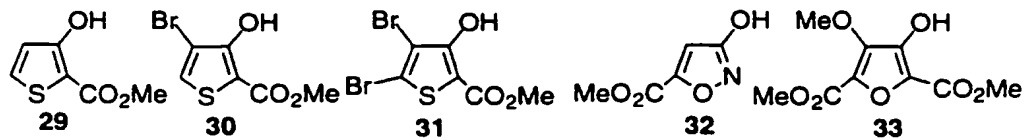
3030

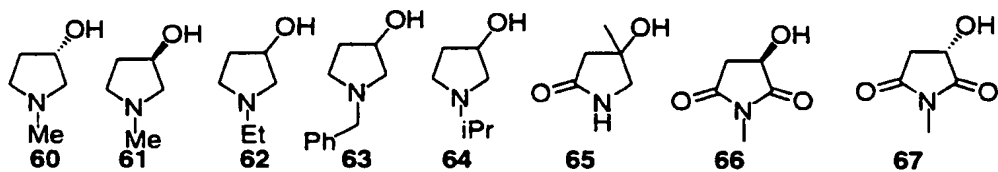
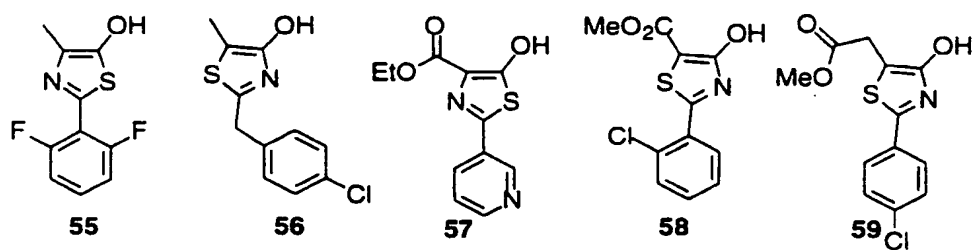
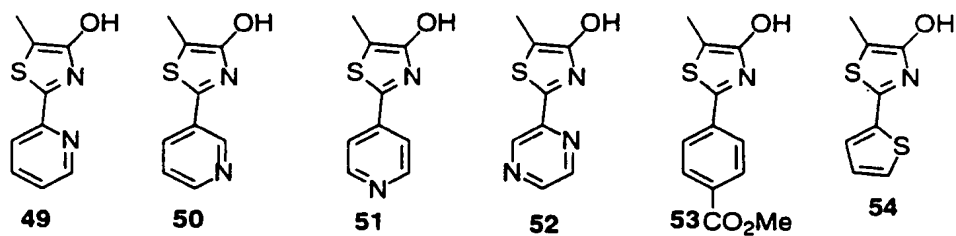
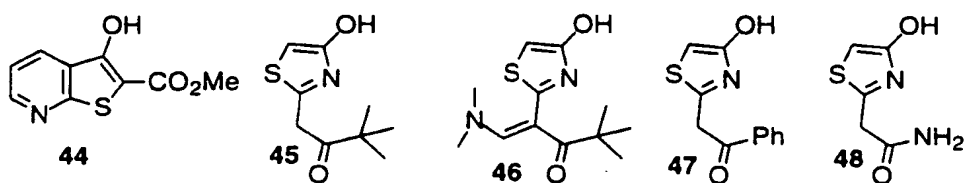
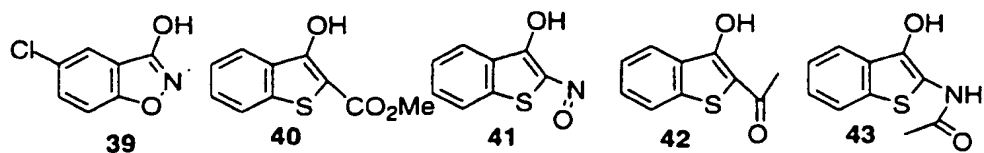
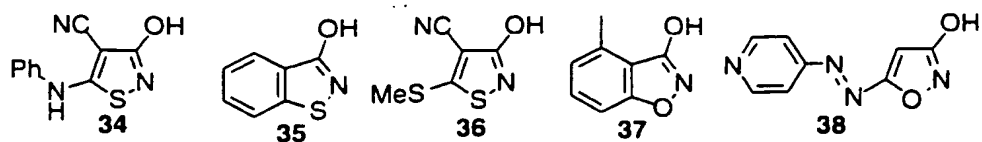


3035

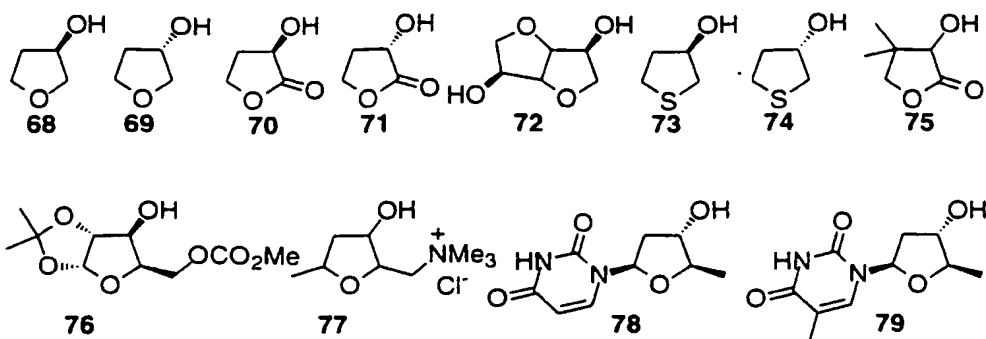


3040

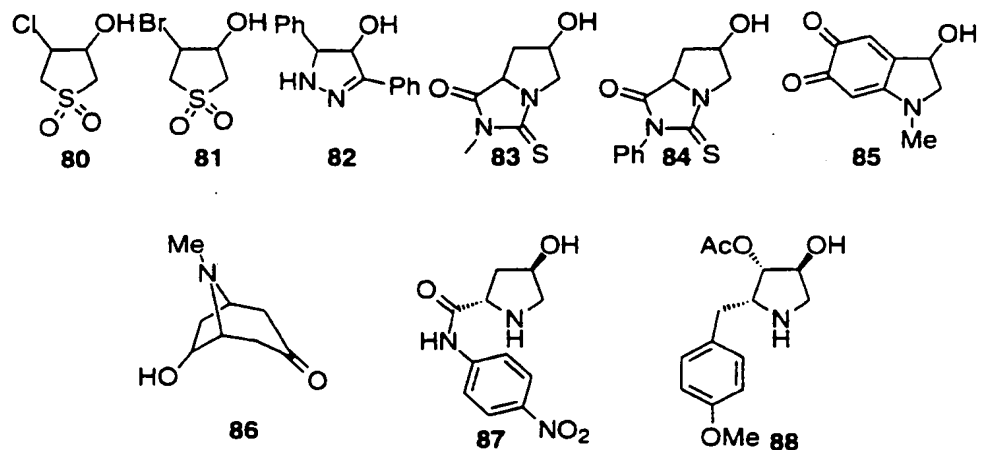




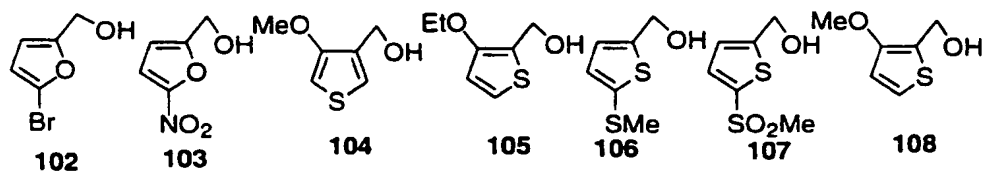
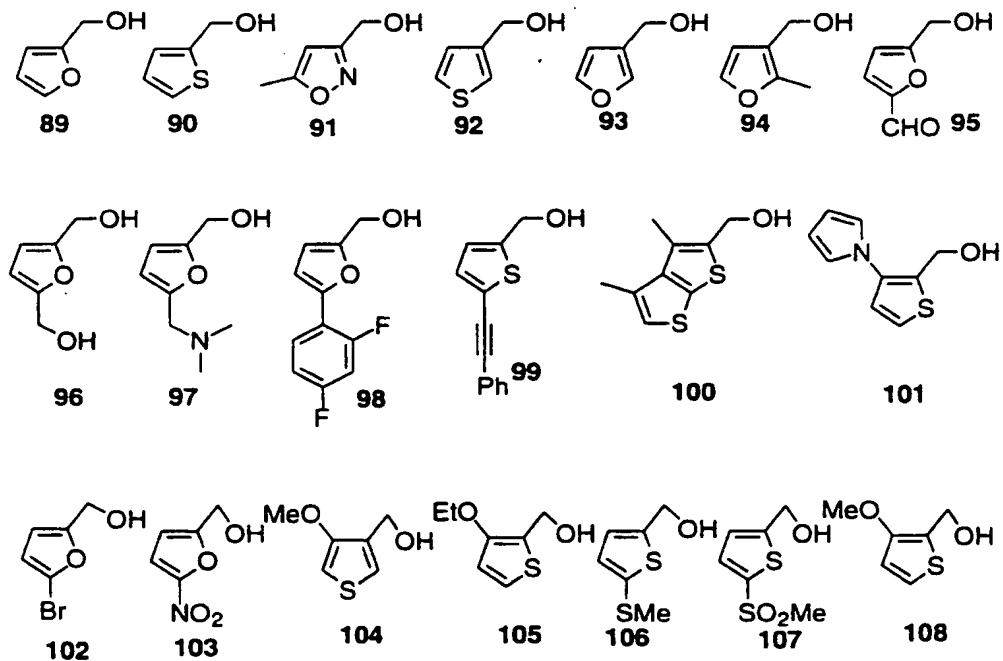
3055

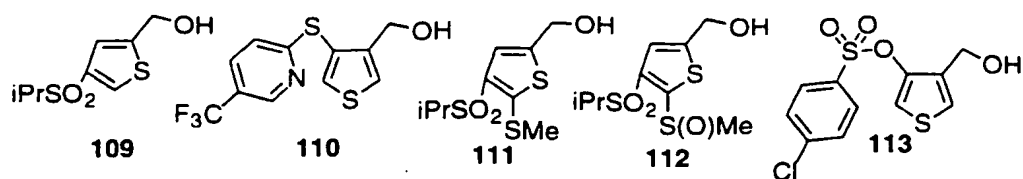


3060

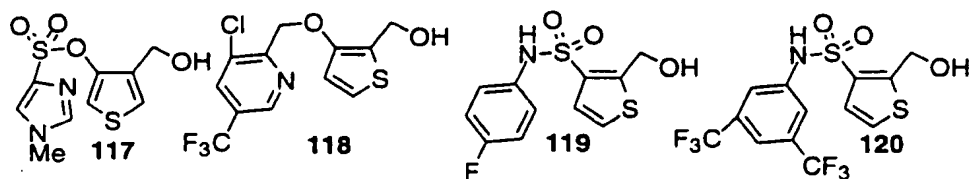
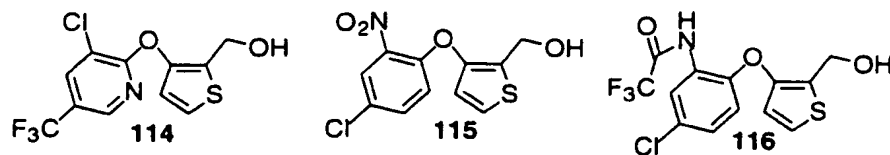


3065

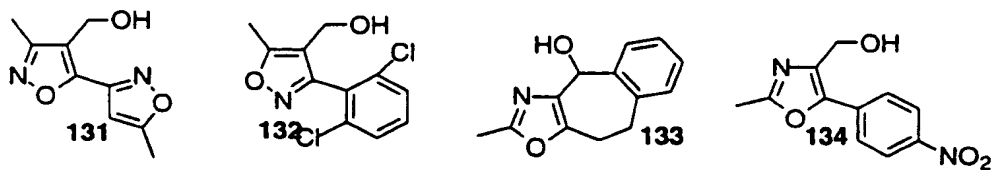
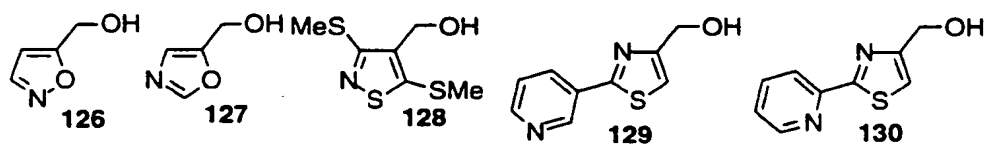
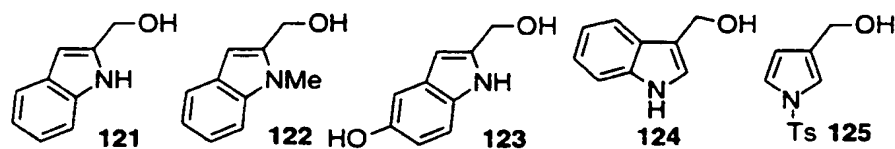




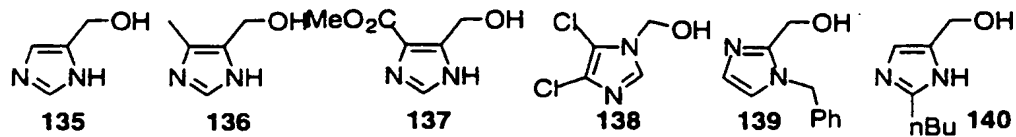
3070

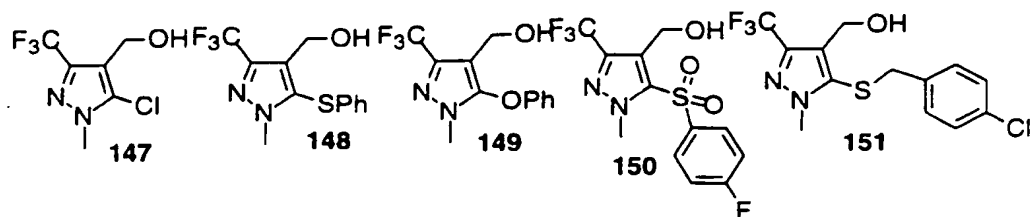
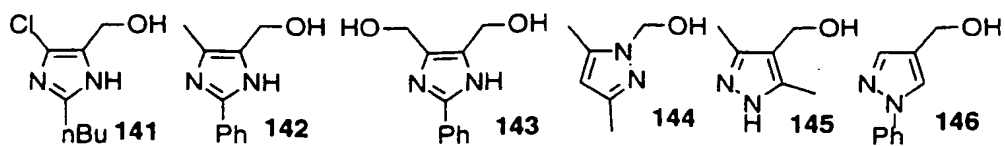


3075

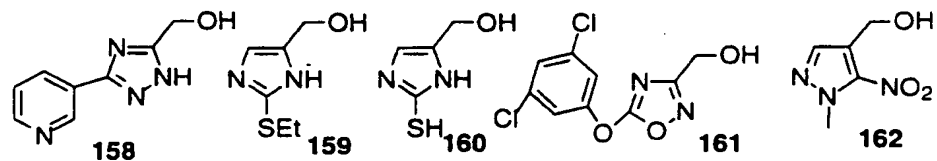
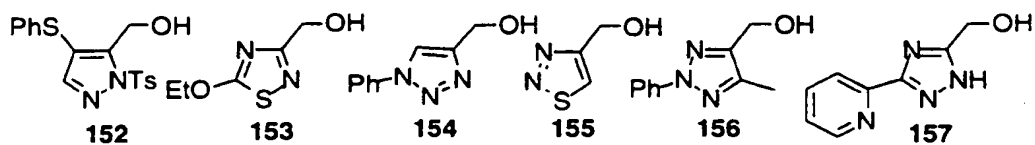


3080

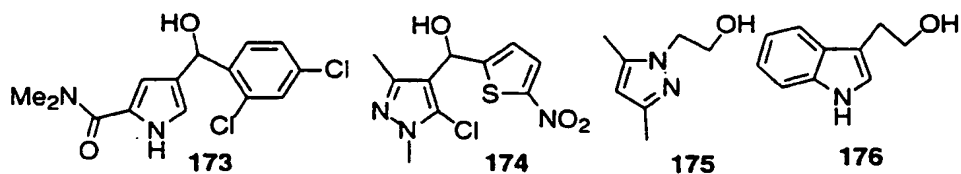
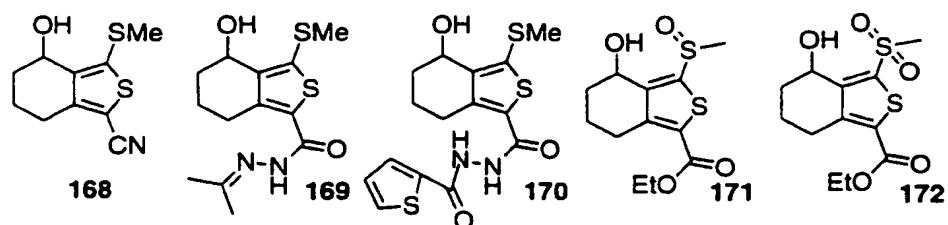
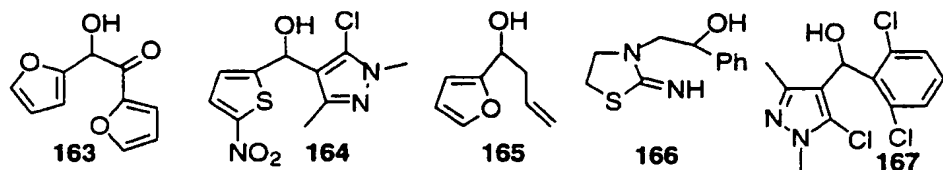




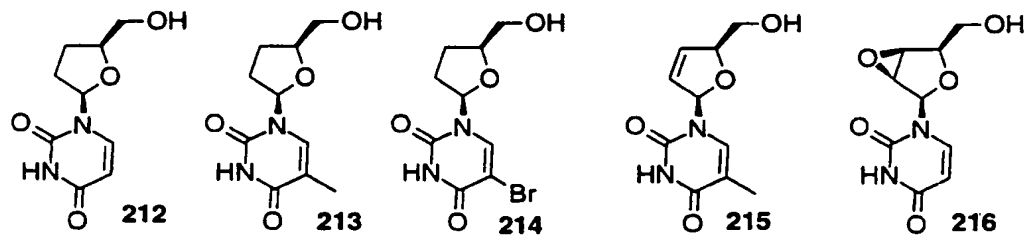
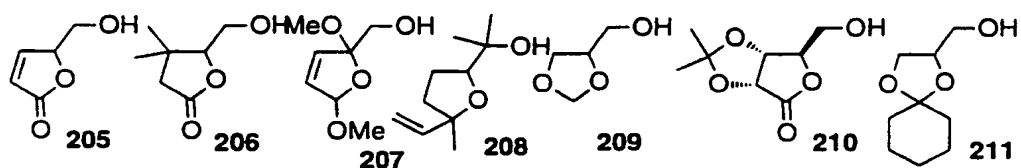
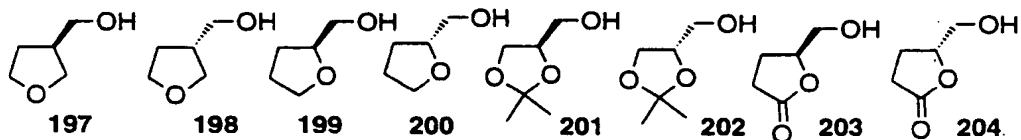
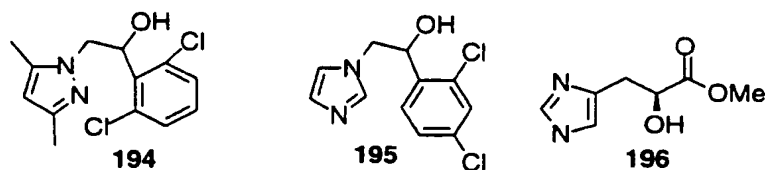
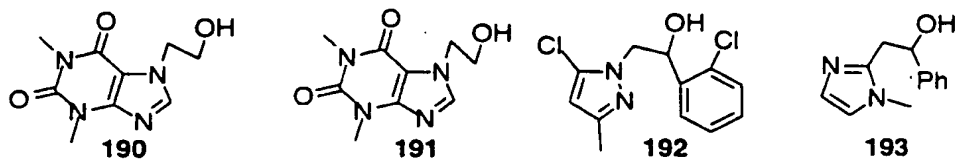
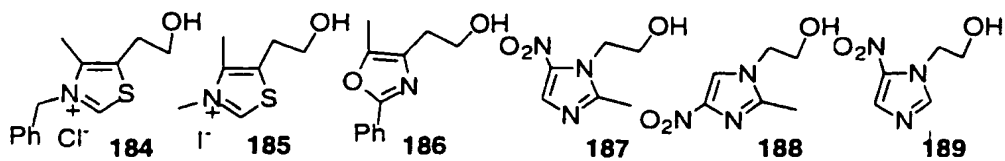
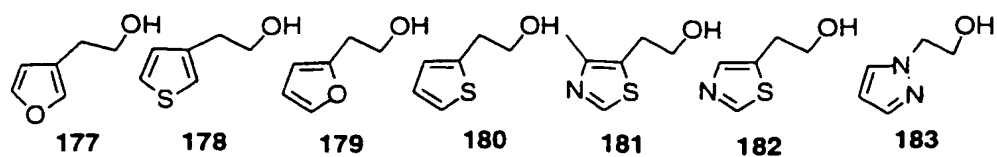
3085

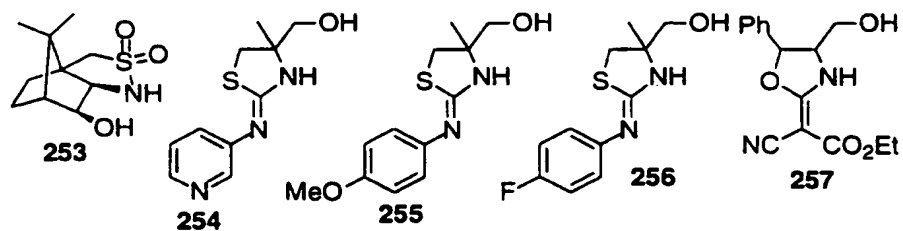
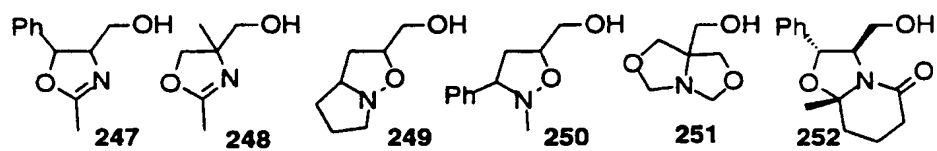
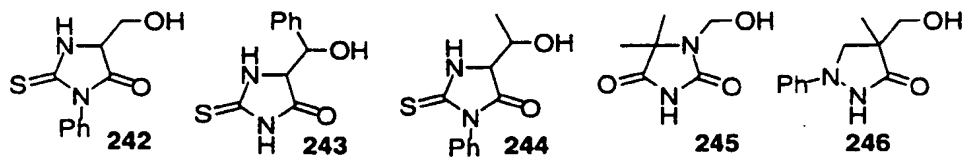
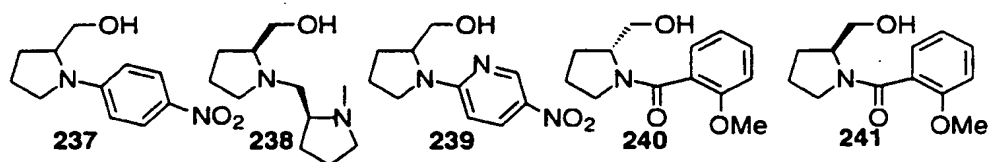
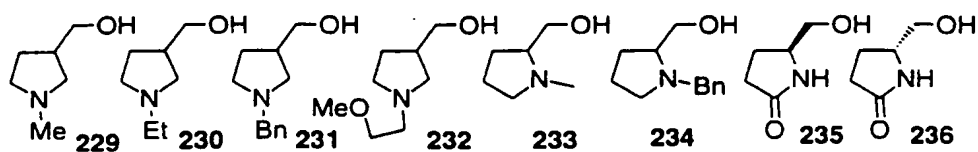
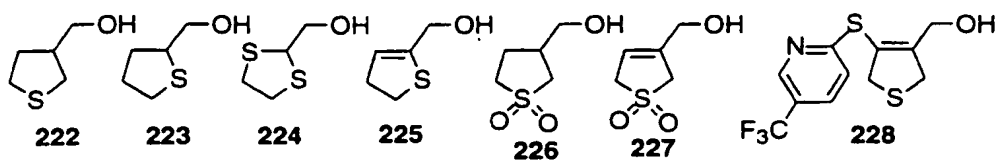
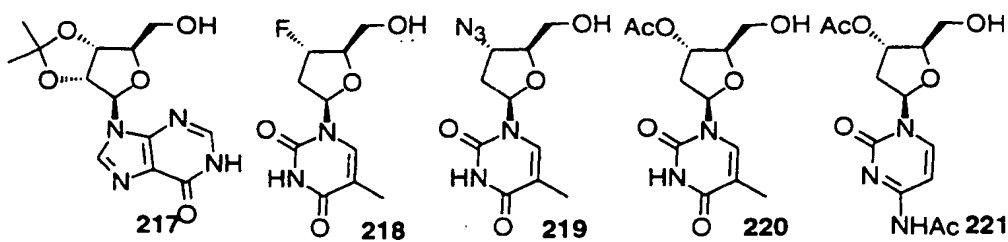


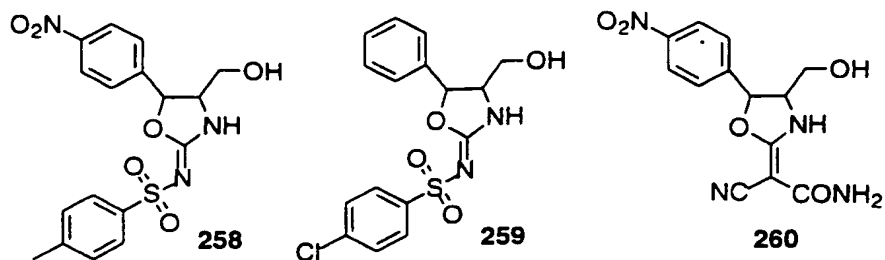
3090



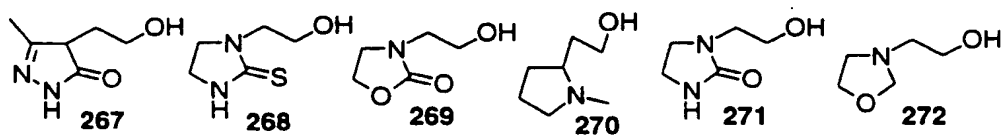
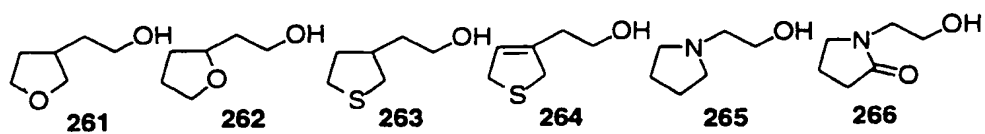
3095



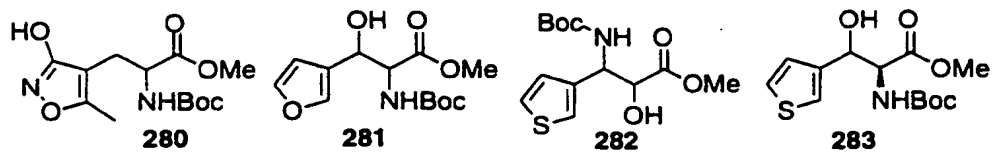
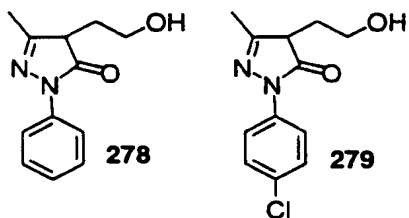
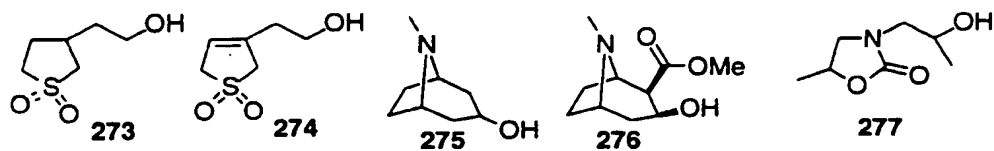




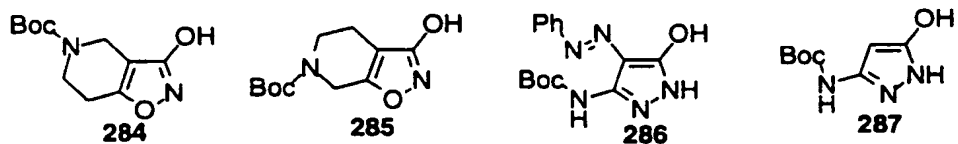
3125

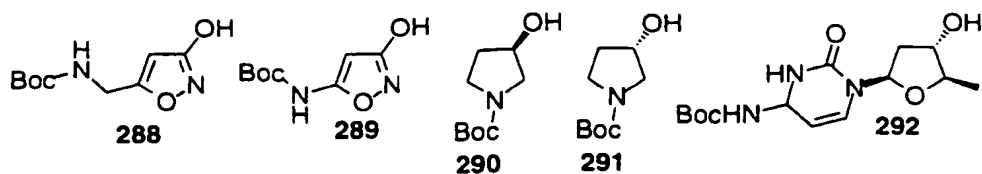


3130

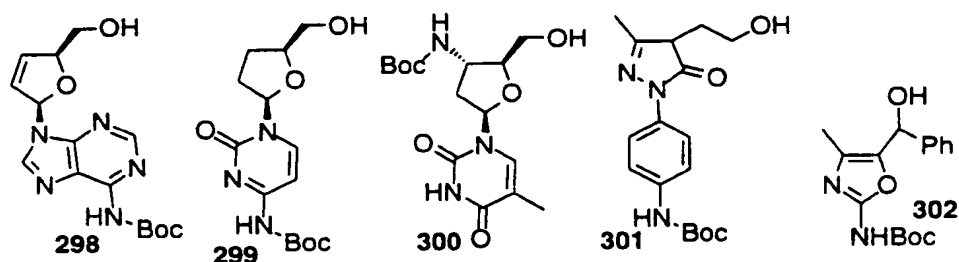
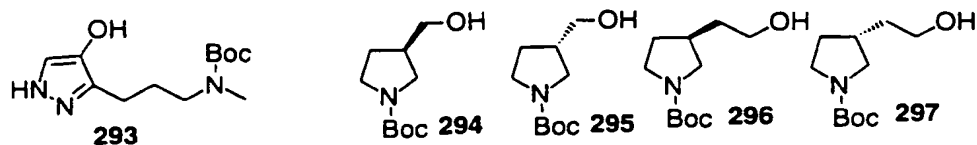


3135

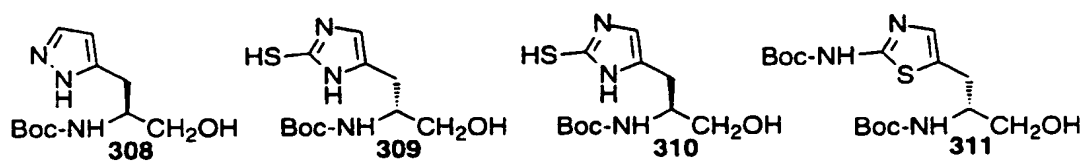
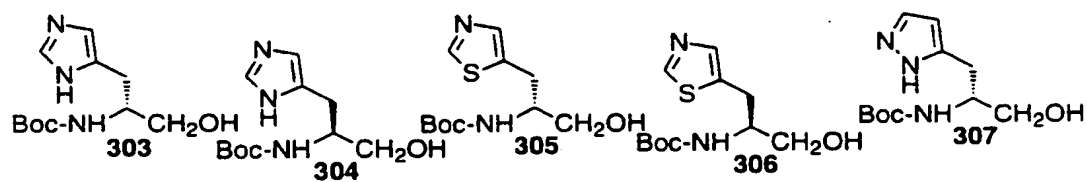




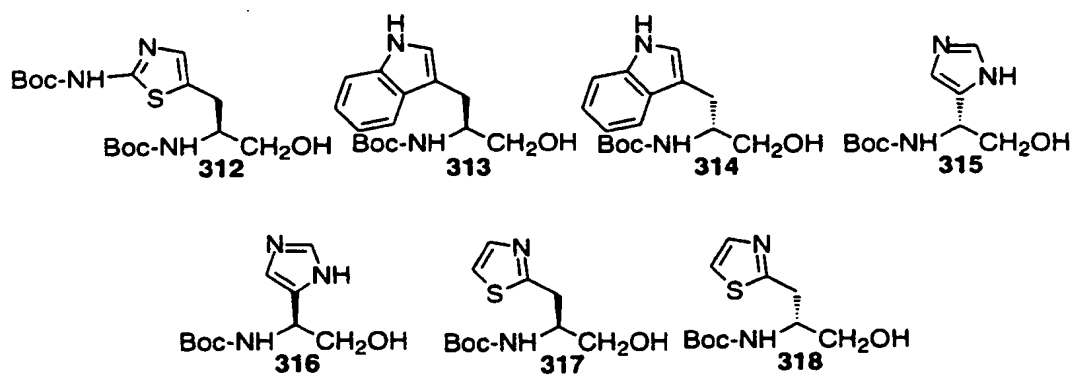
3140

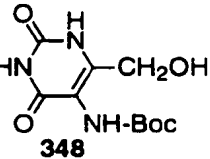
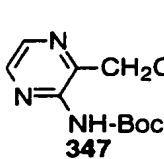
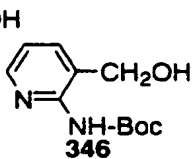
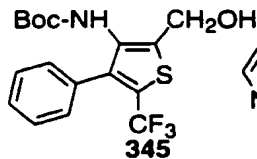
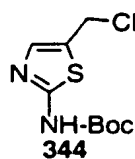
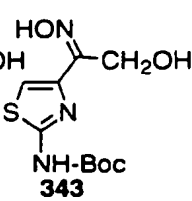
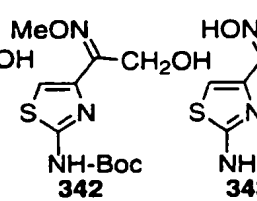
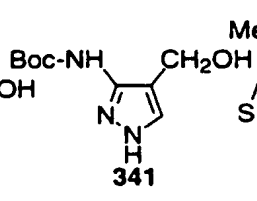
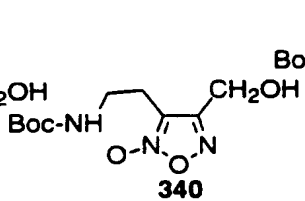
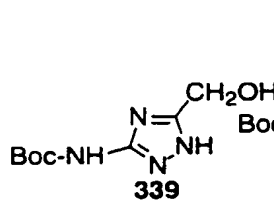
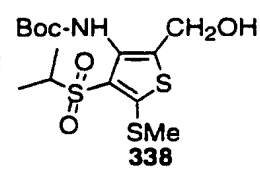
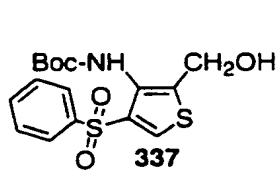
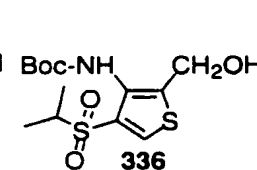
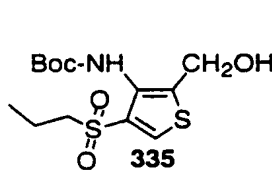
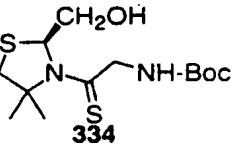
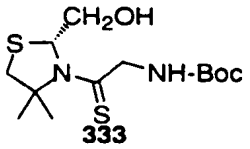
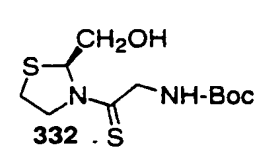
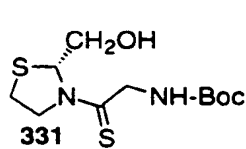
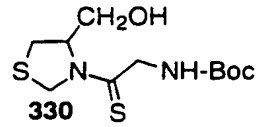
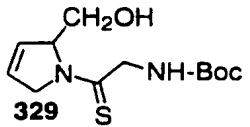
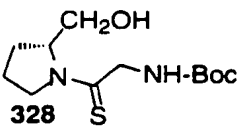
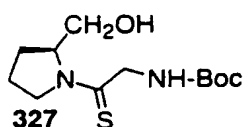
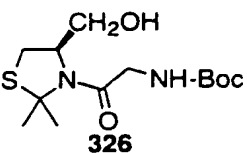
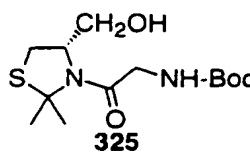
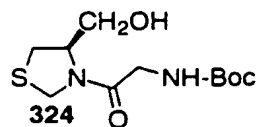
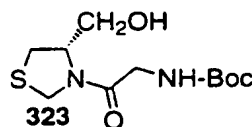
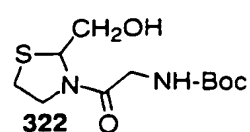
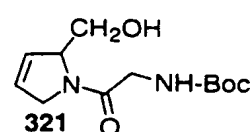
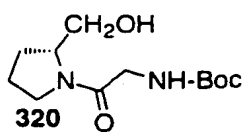
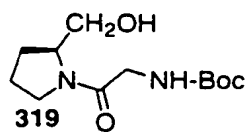


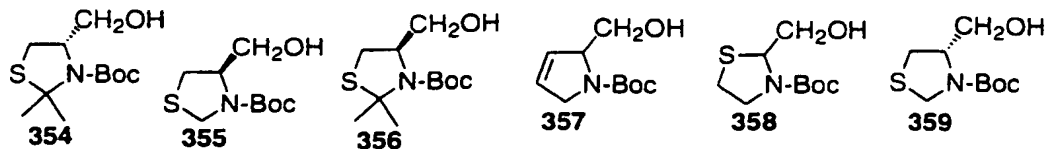
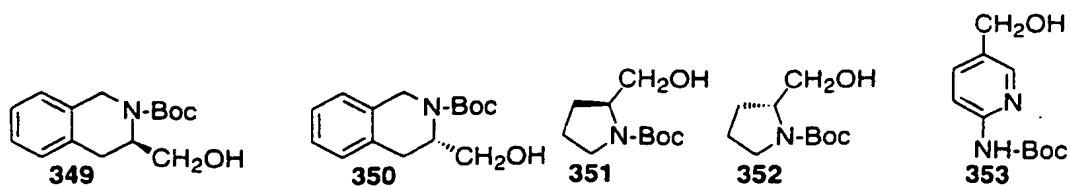
3145



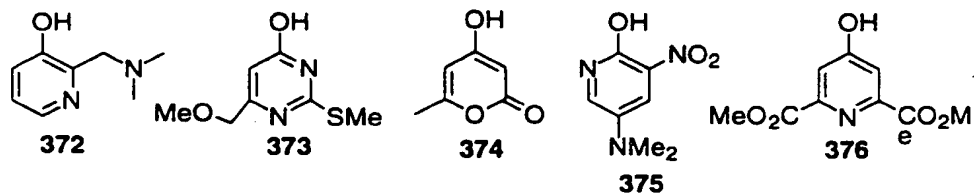
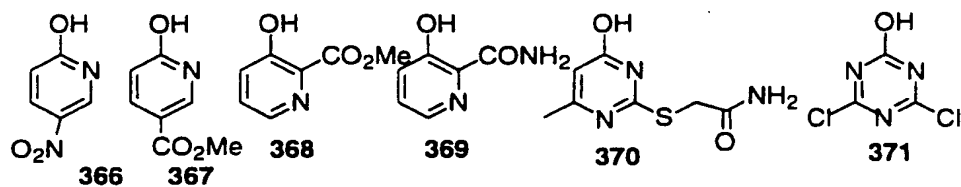
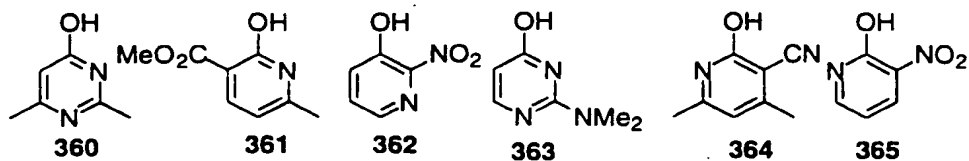
3150



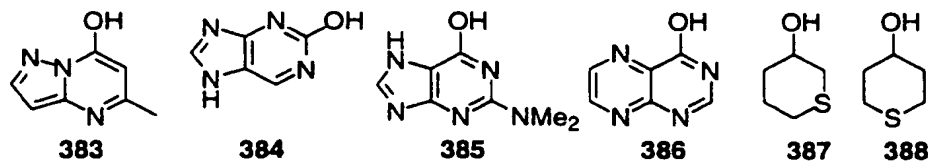
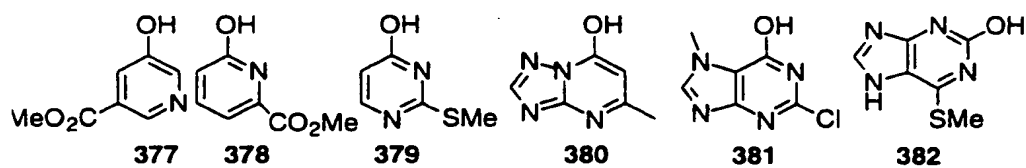




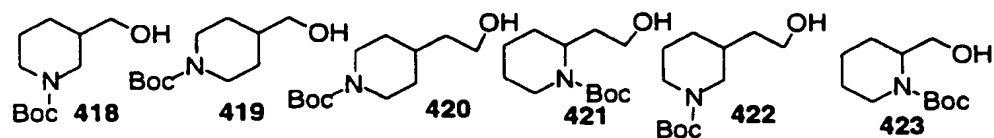
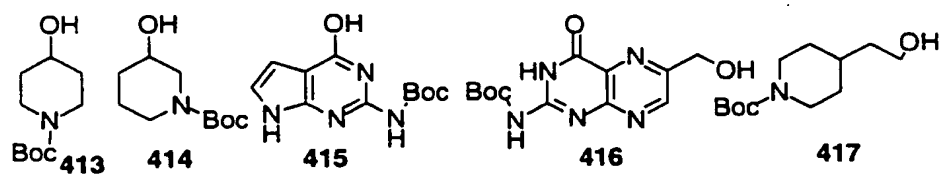
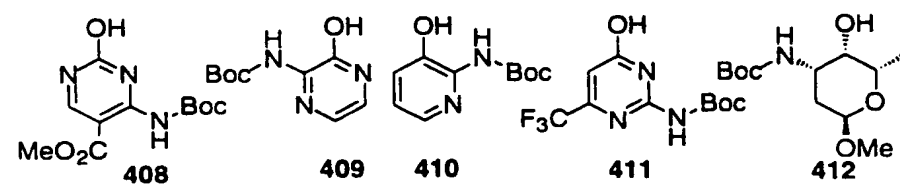
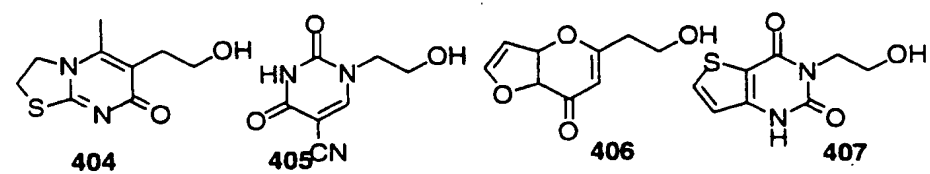
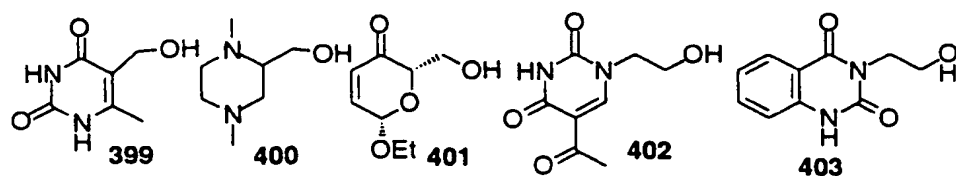
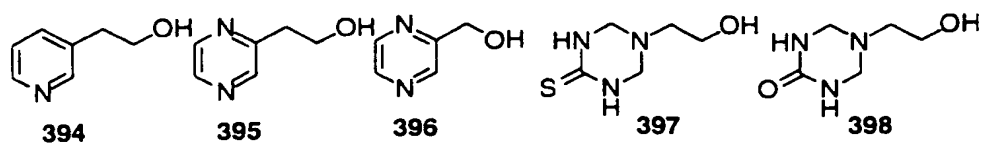
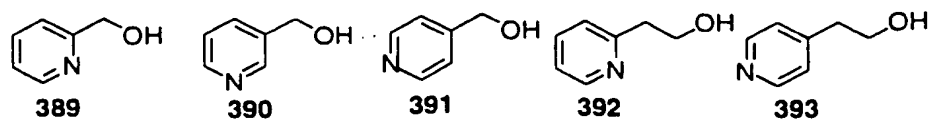
3170



3175



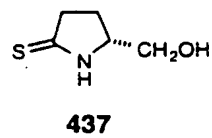
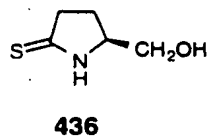
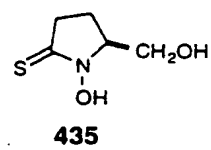
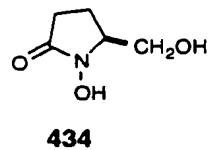
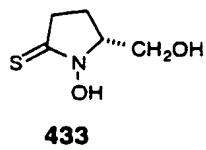
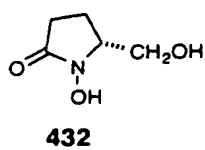
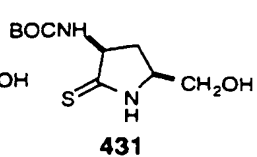
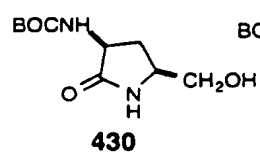
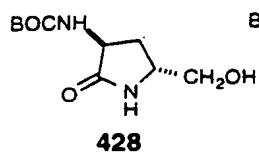
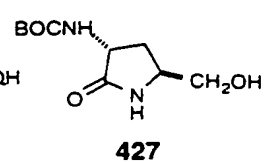
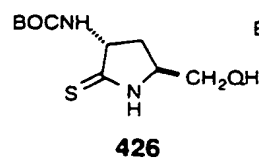
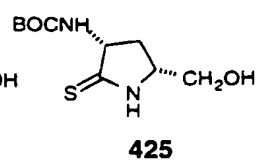
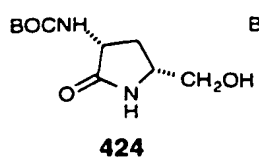
3180



3185

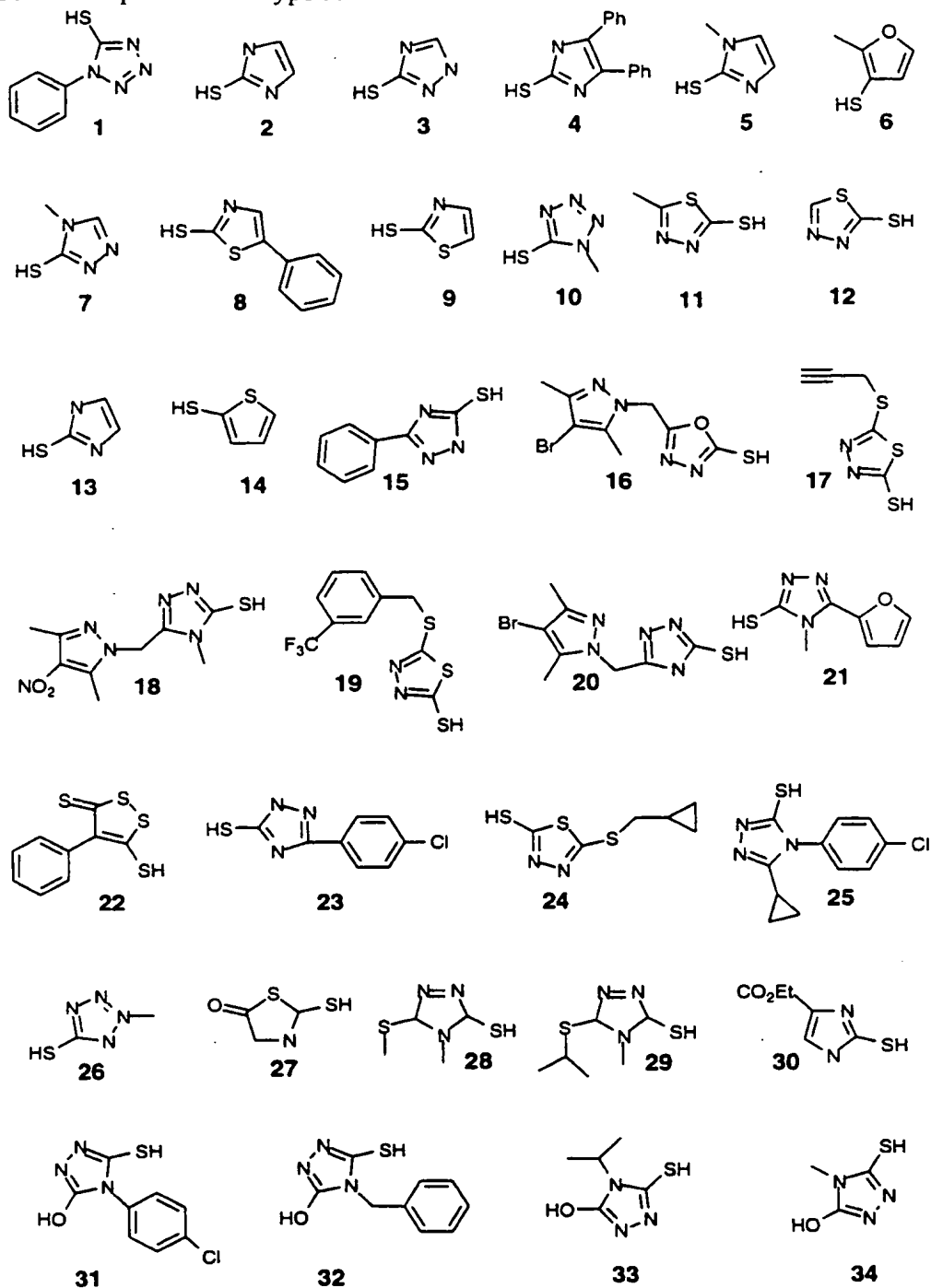
3190

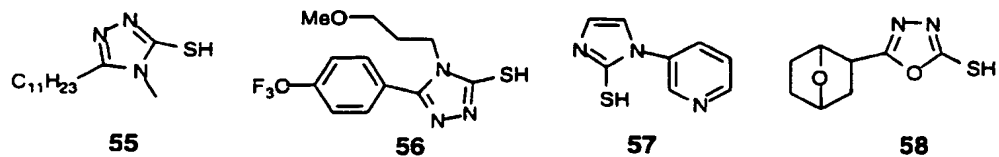
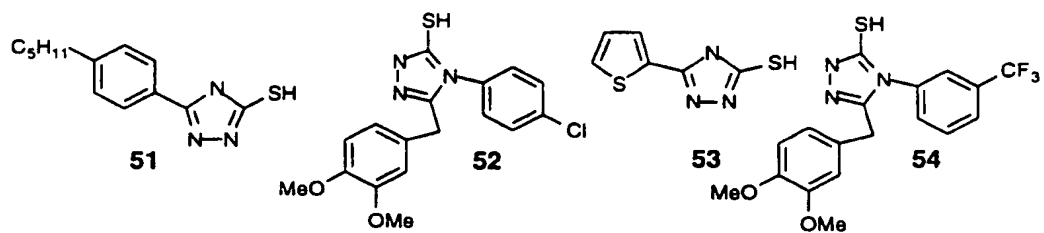
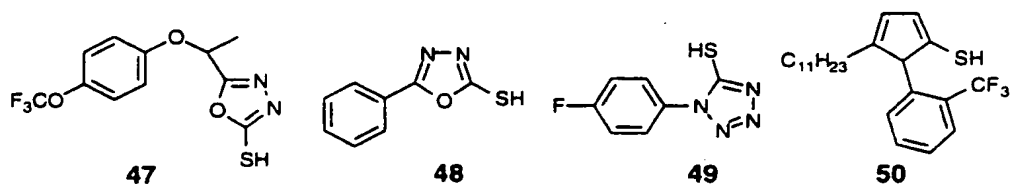
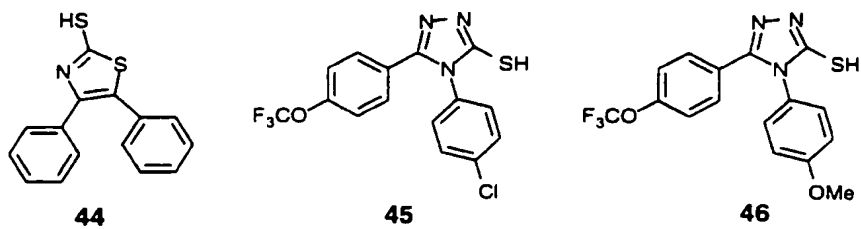
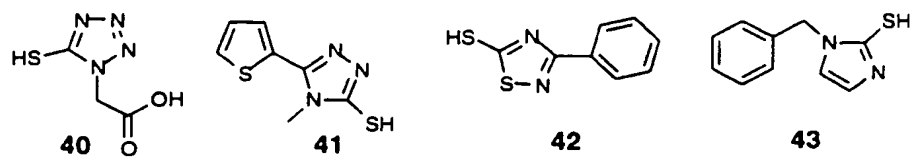
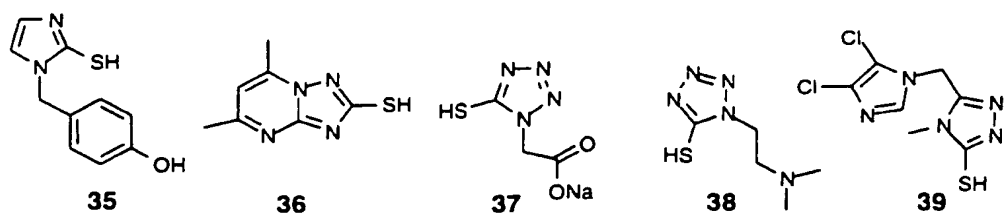
3195

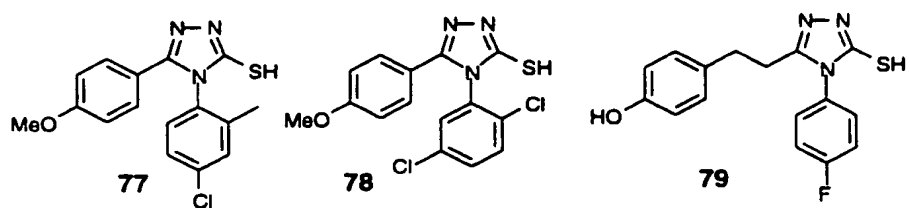
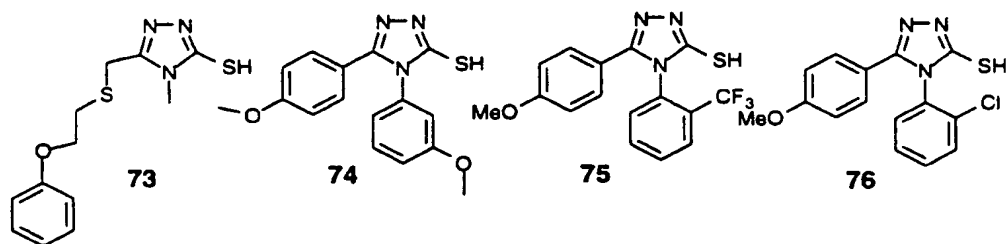
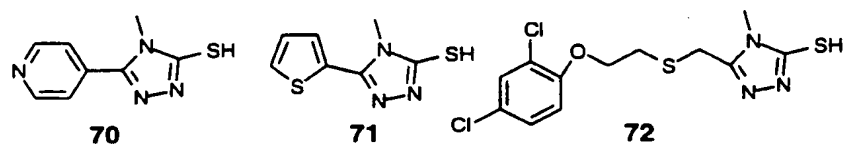
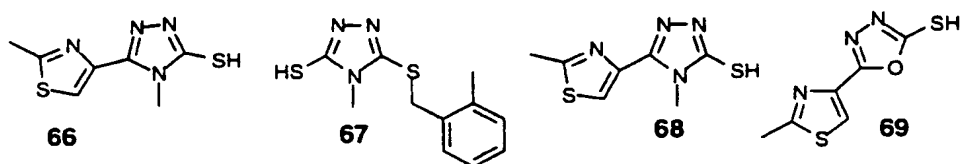
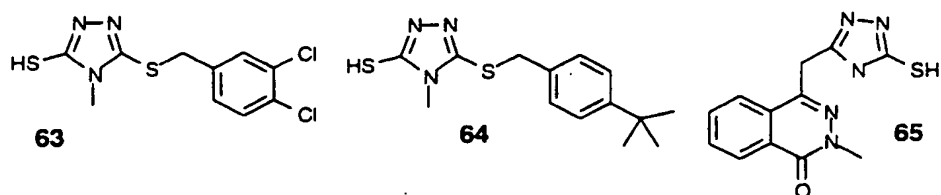
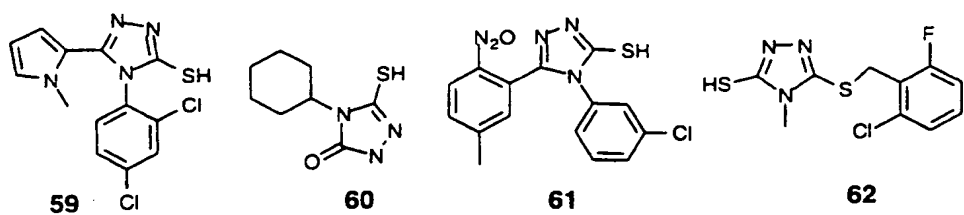


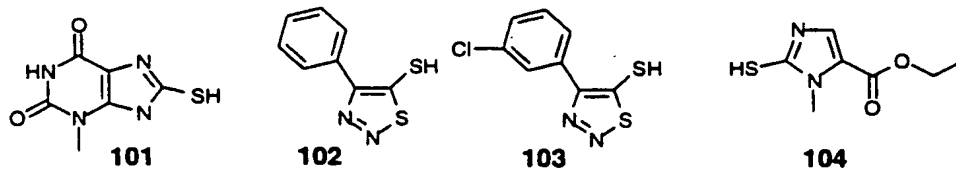
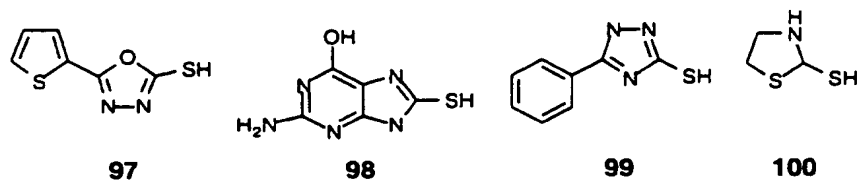
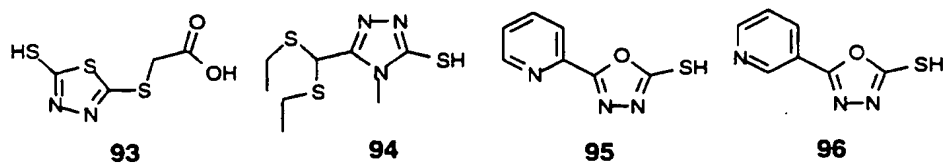
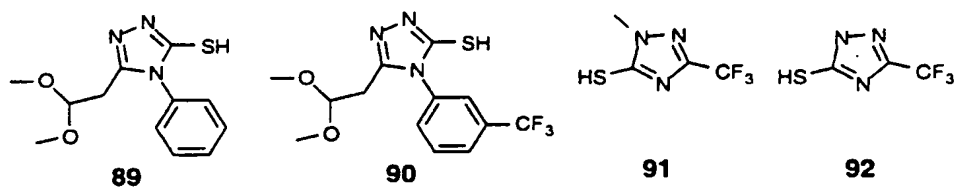
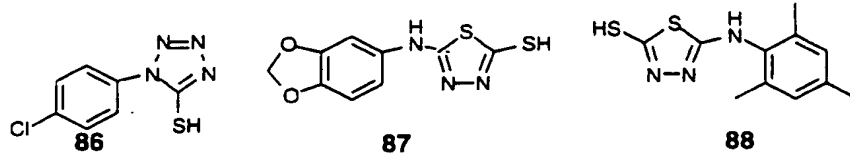
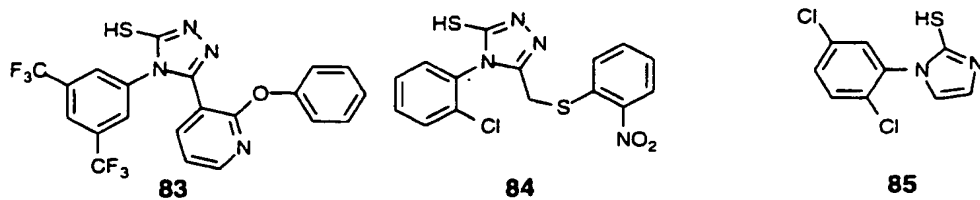
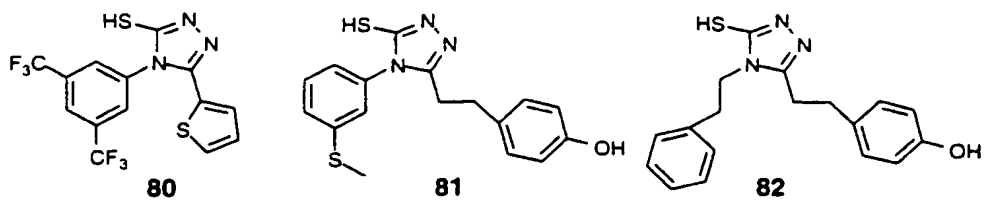
3200

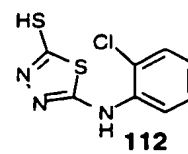
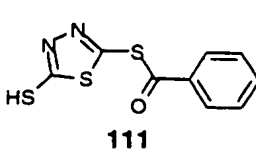
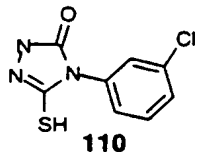
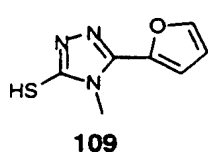
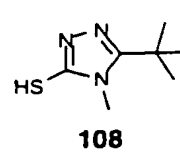
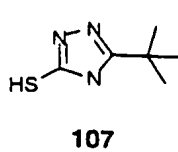
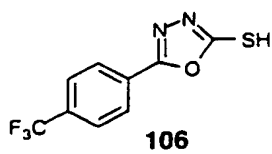
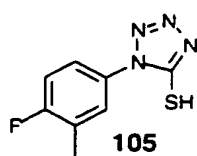
Table 16. Mercaptans of the type A-SH



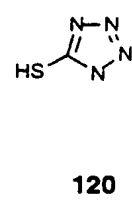
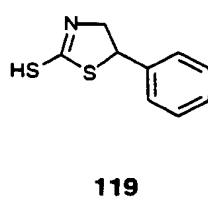
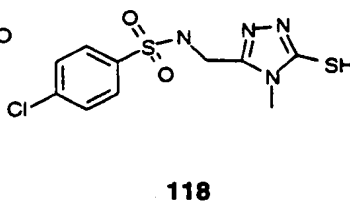
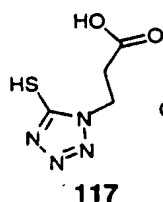
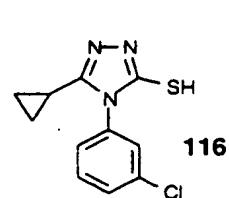
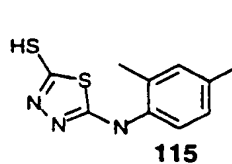
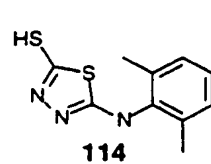
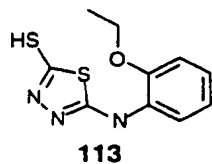




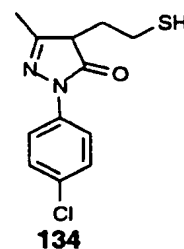
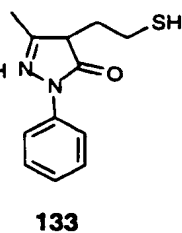
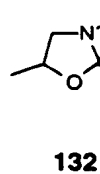
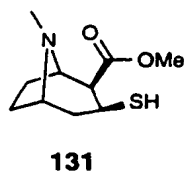
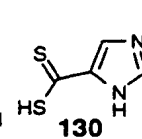
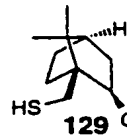
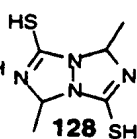
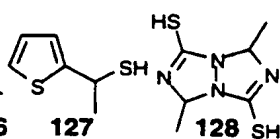
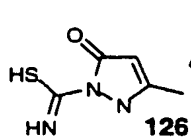
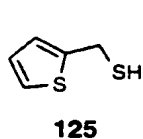
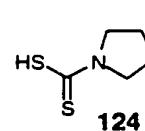
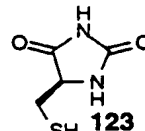
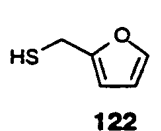
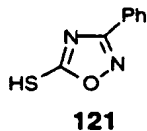
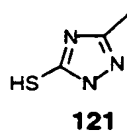




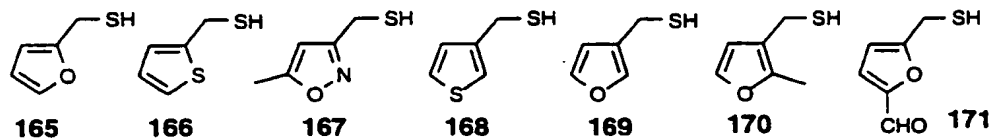
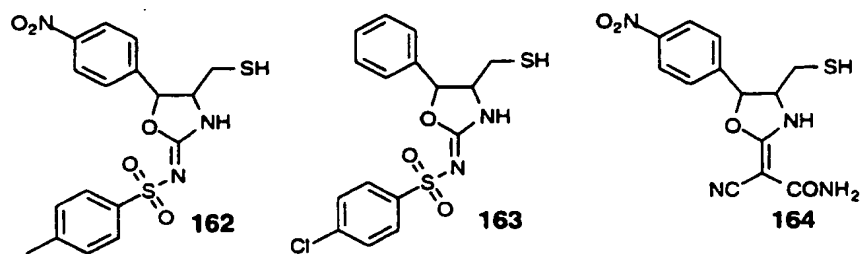
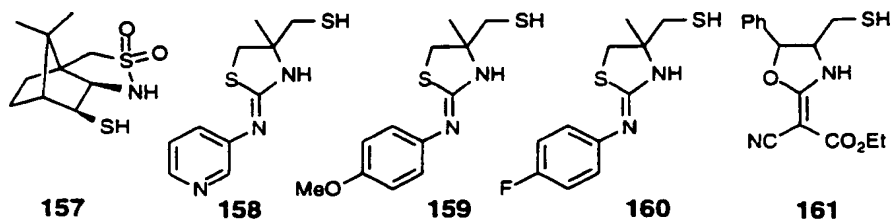
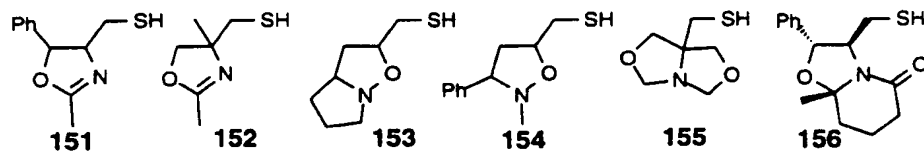
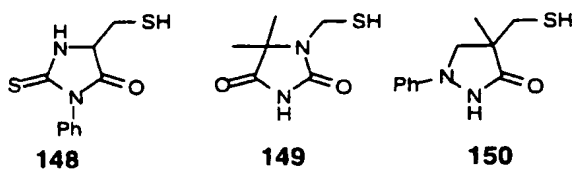
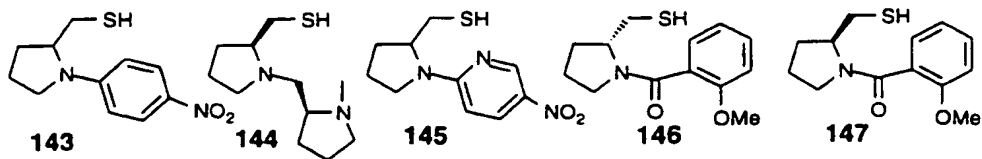
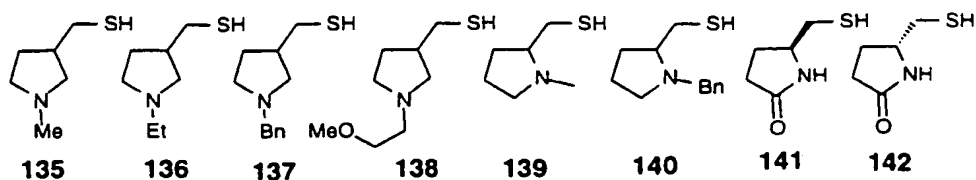
3260



3265

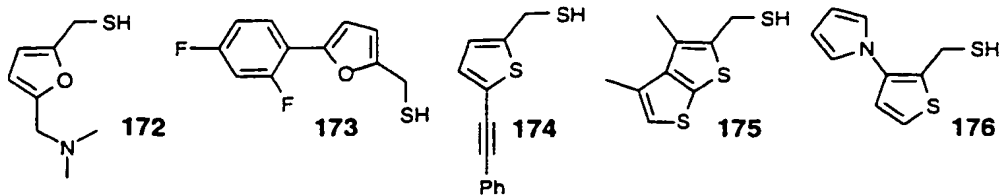


3270

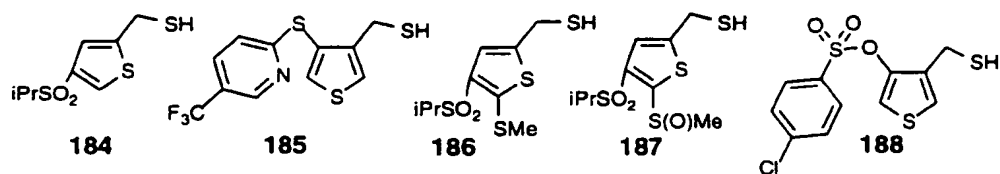
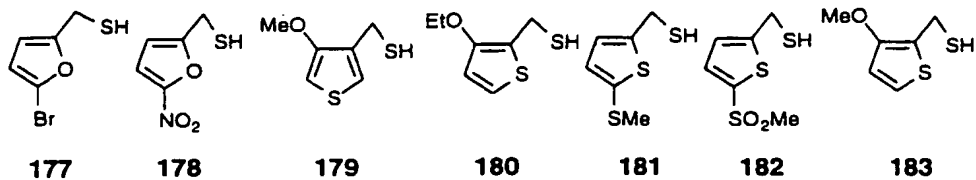


3275

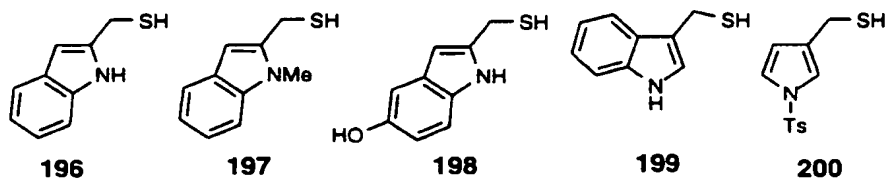
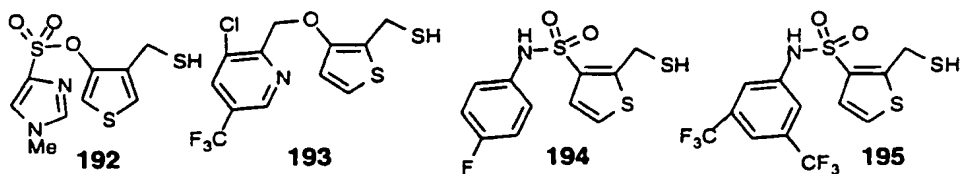
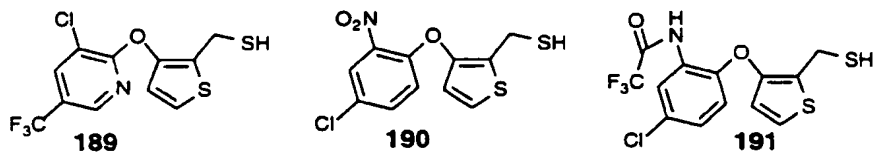
3280



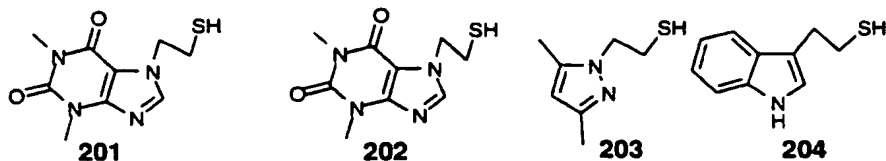
3285

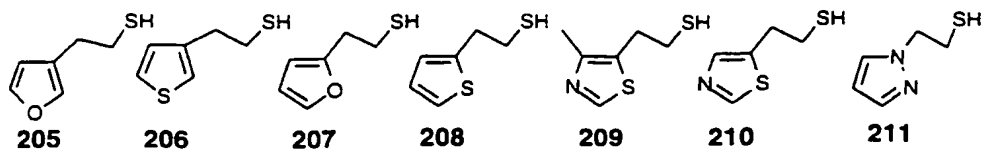


3290

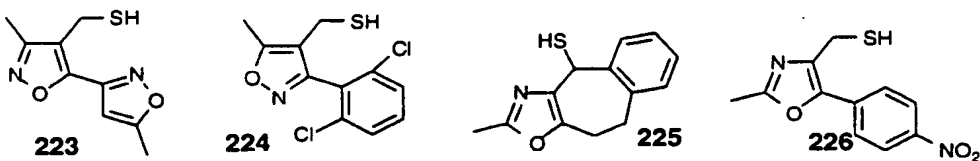
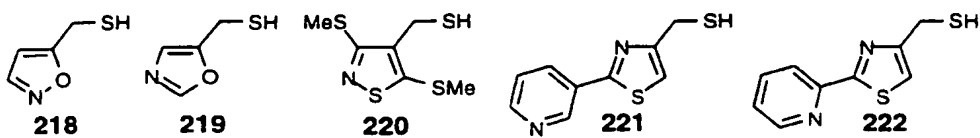
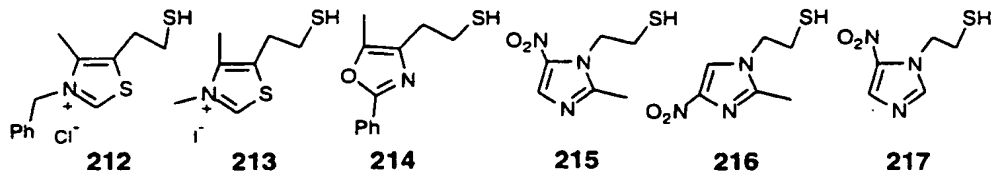


3295

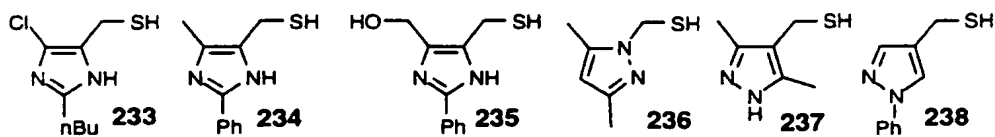
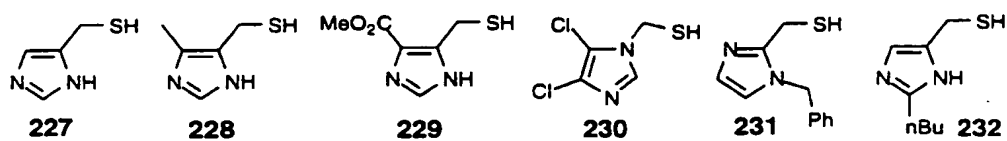




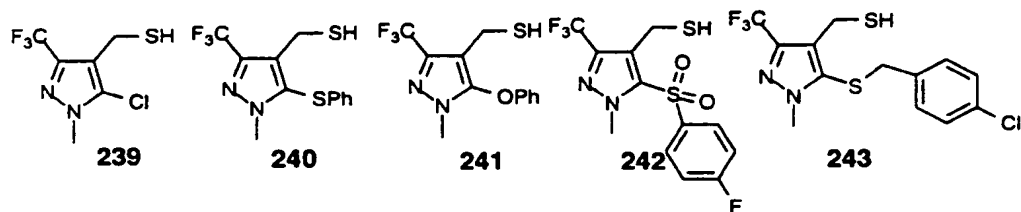
3300

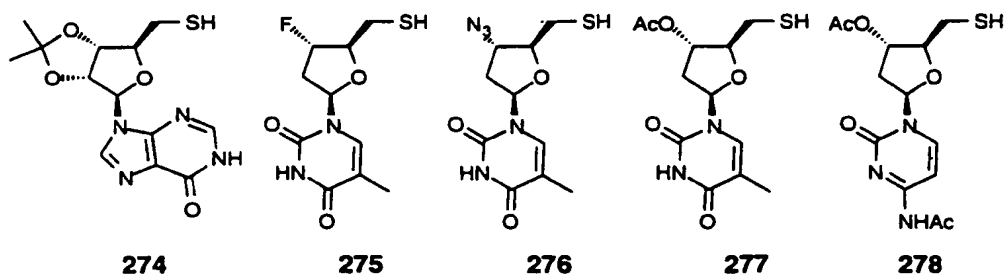
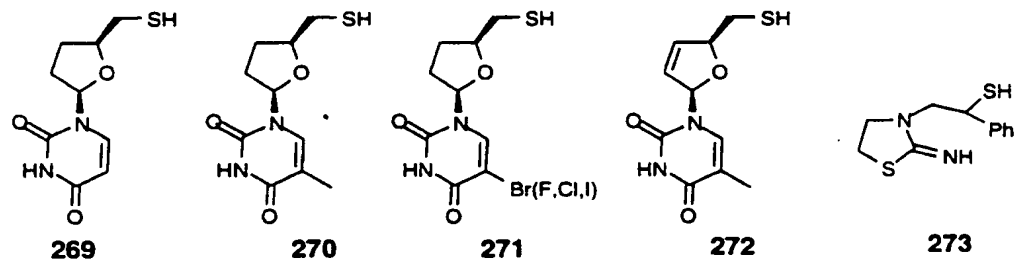
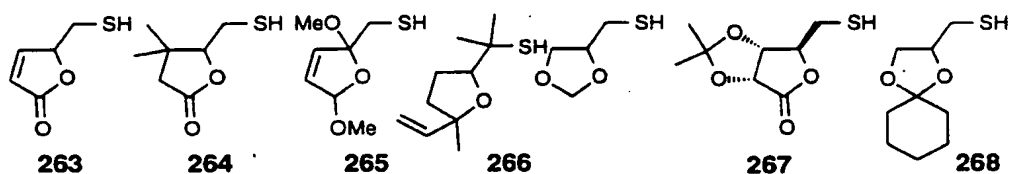
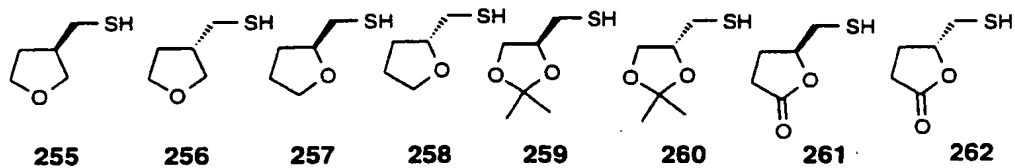
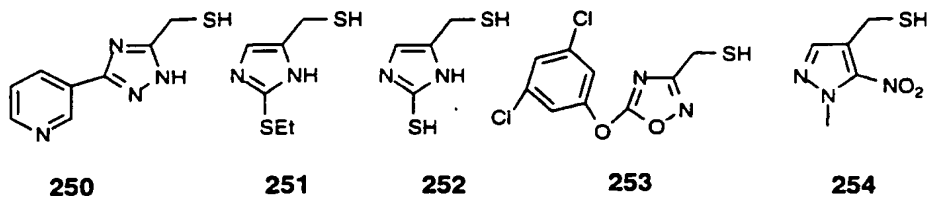
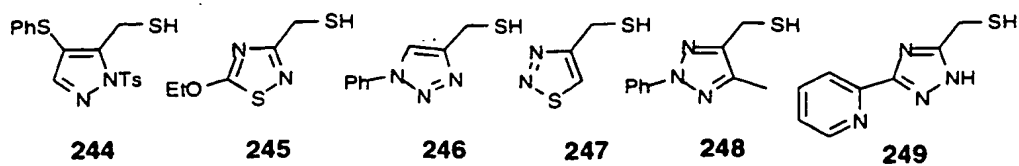


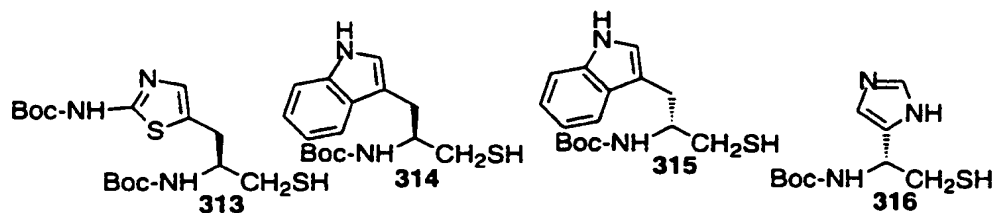
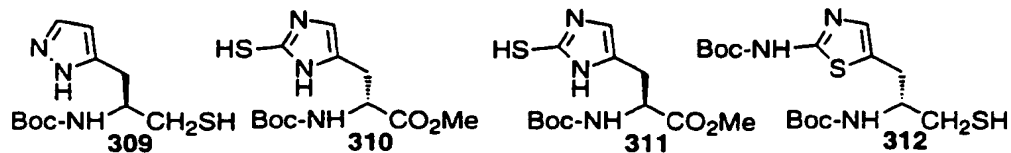
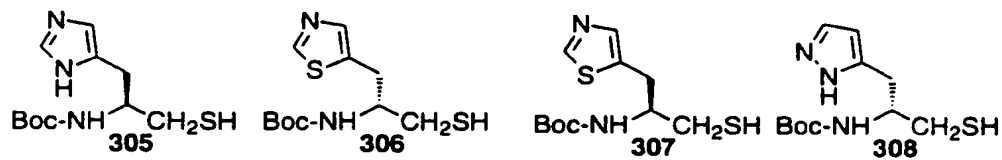
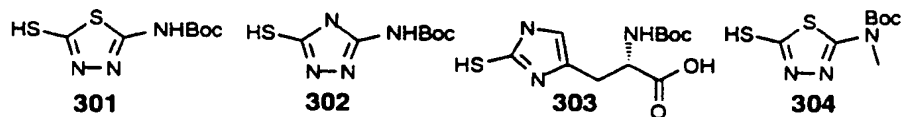
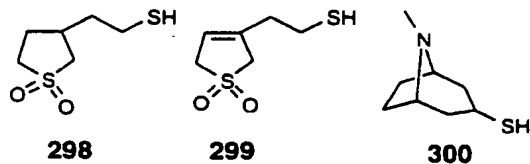
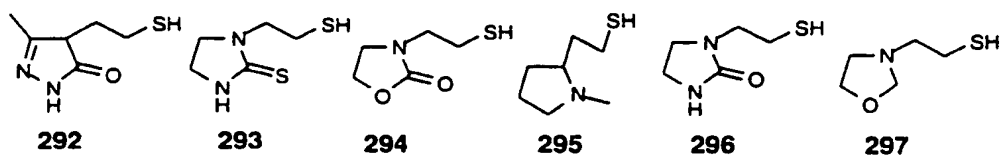
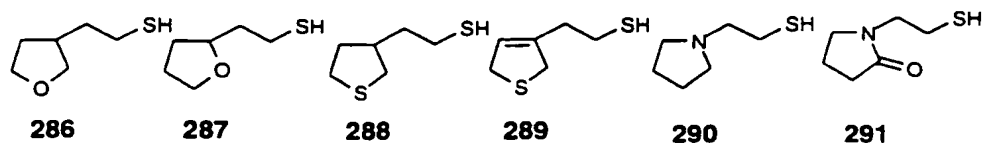
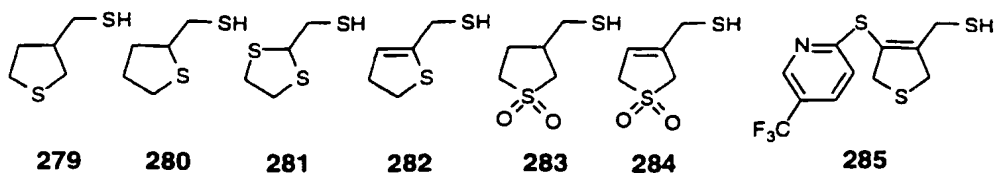
3305



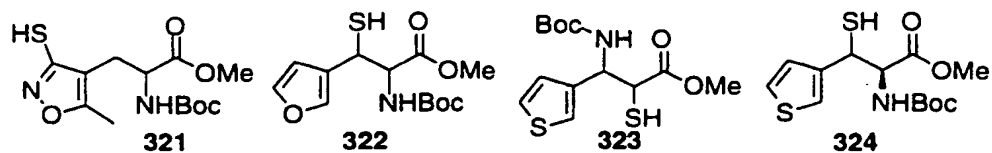
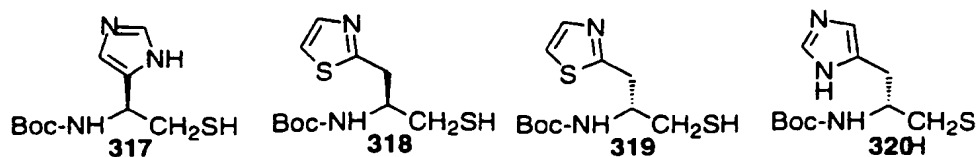
3310



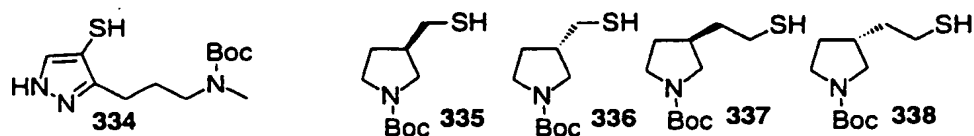
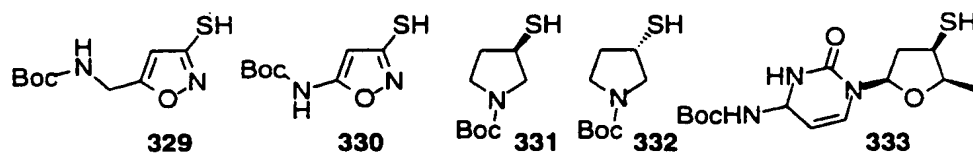
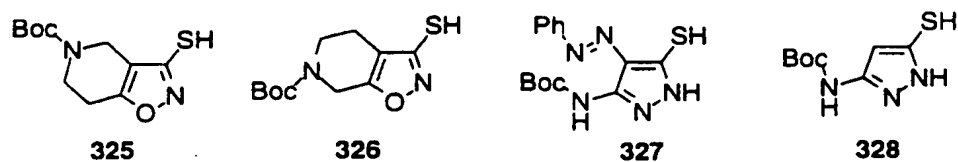




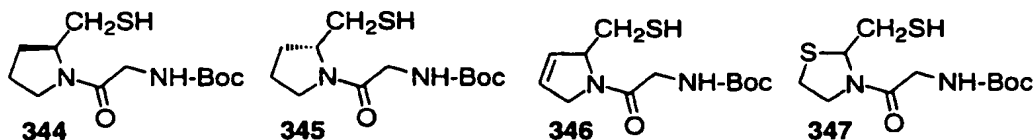
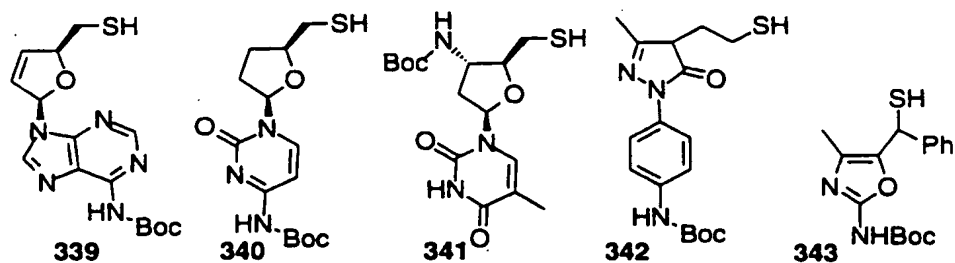
3340



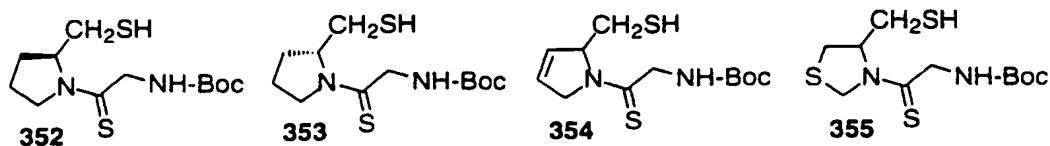
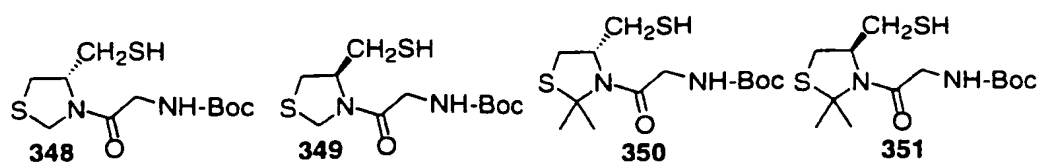
3345



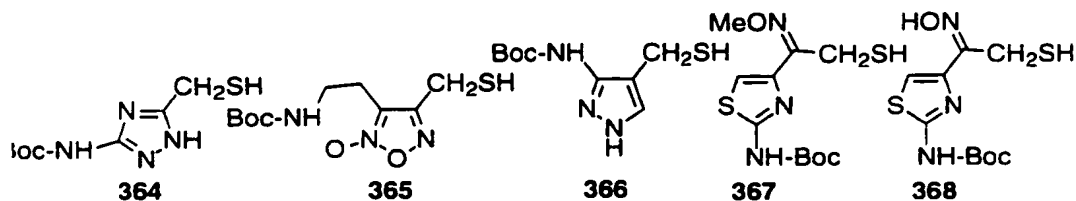
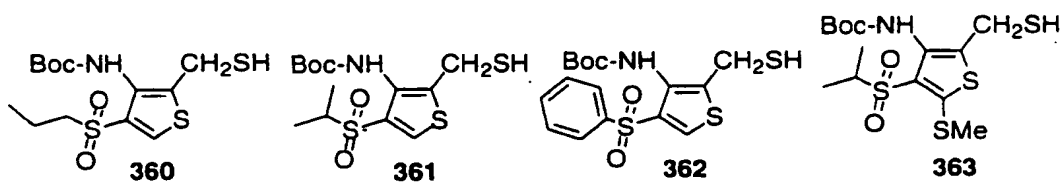
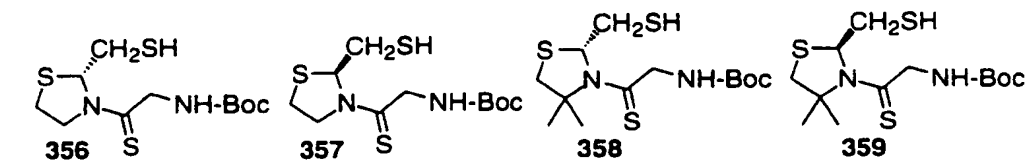
3350



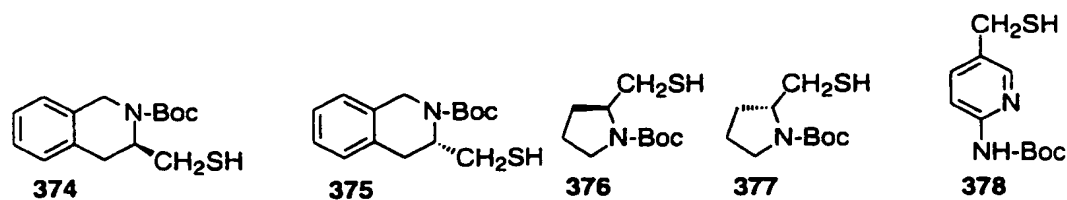
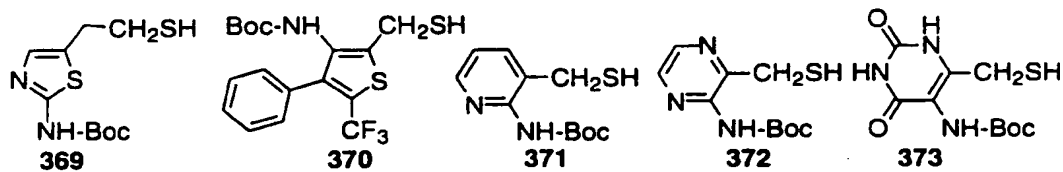
3355

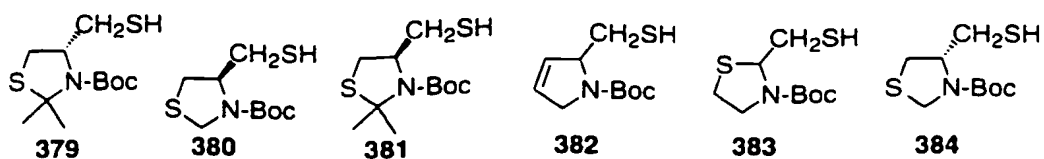


3360

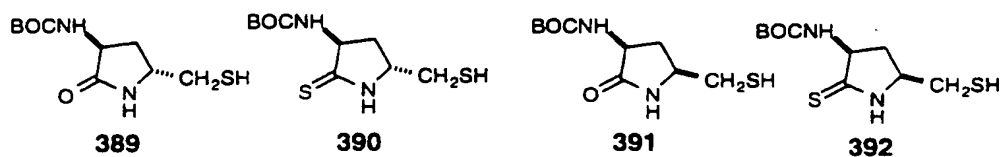
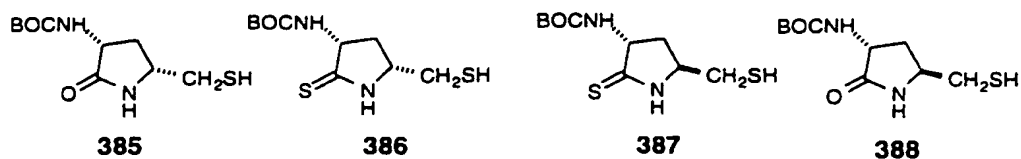


3365

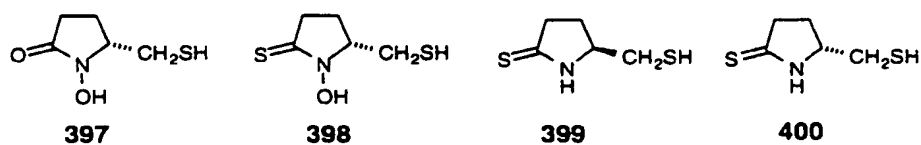
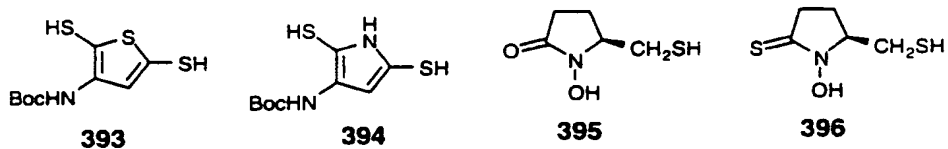




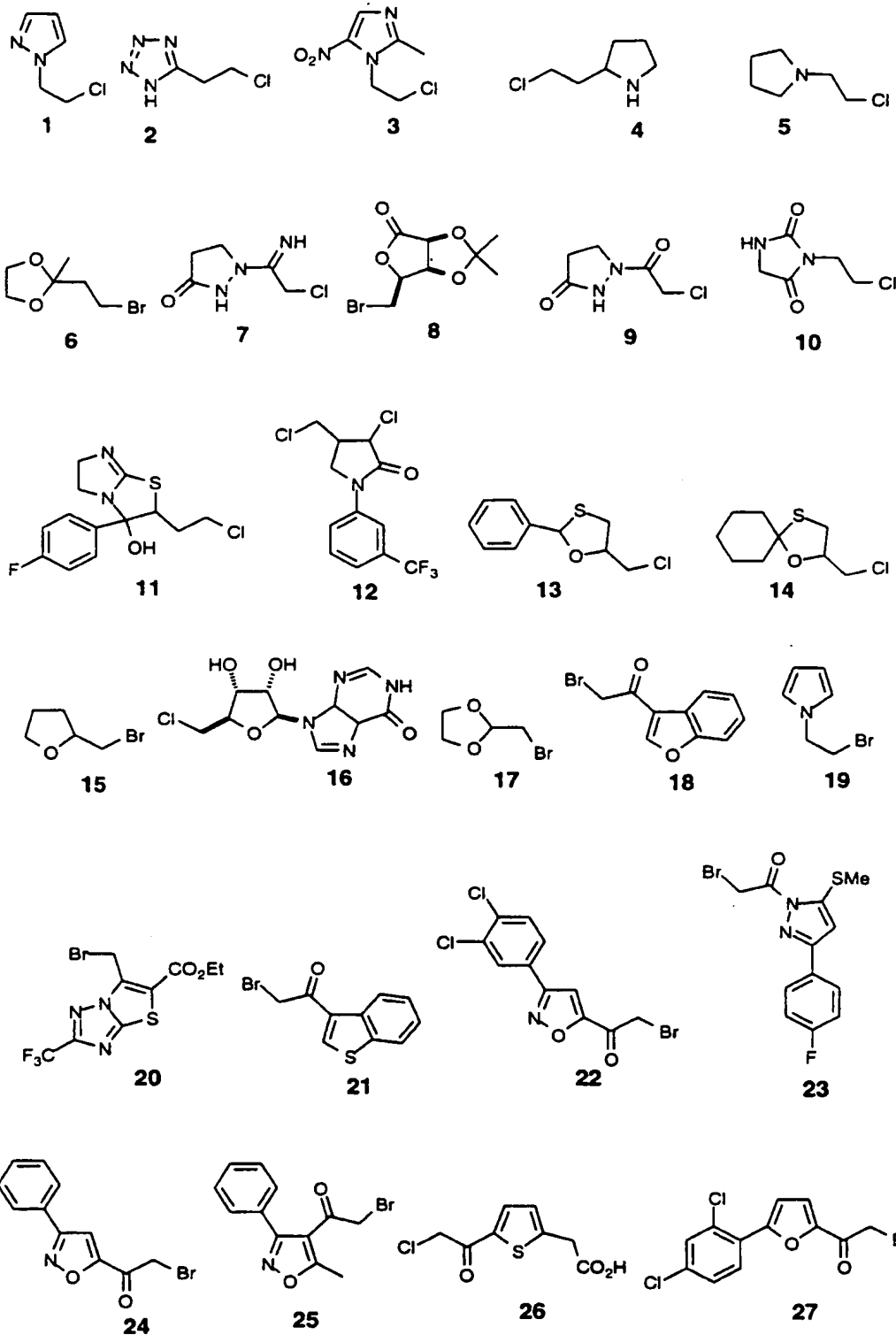
3370

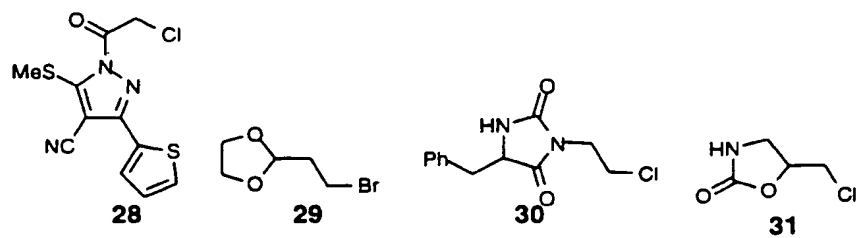


3375

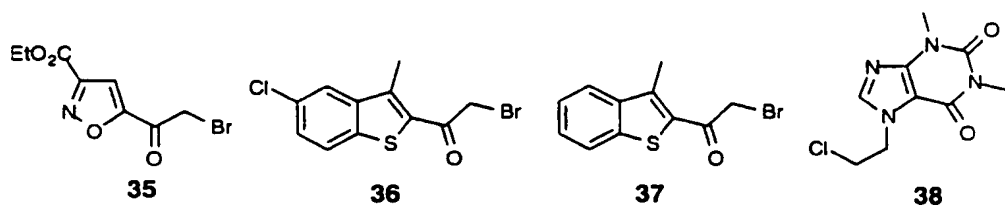
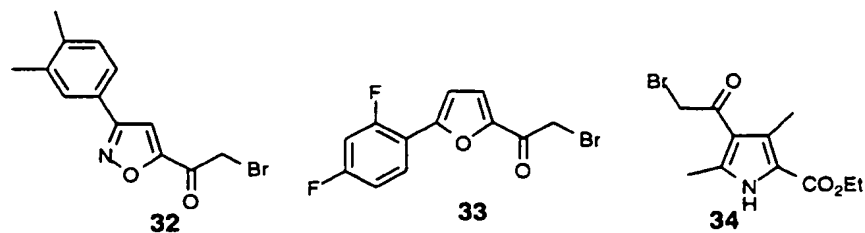


3380 Table 17. Halides of the type A-Cl, A-Br, and A-I

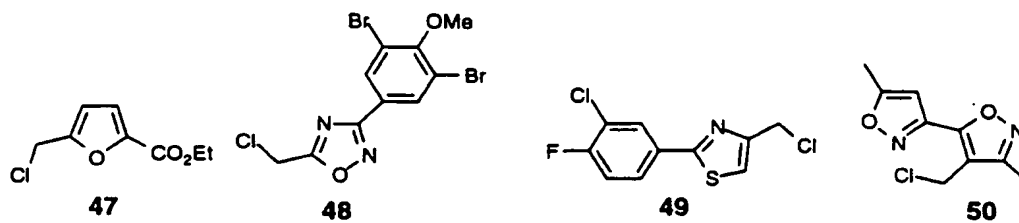
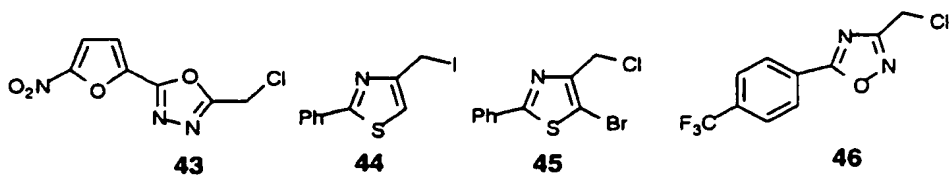
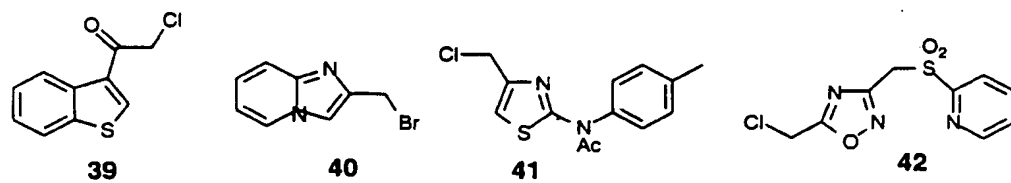




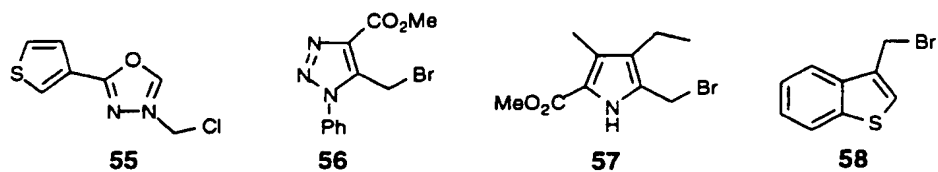
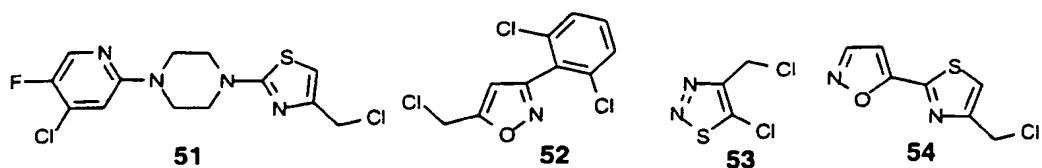
3395



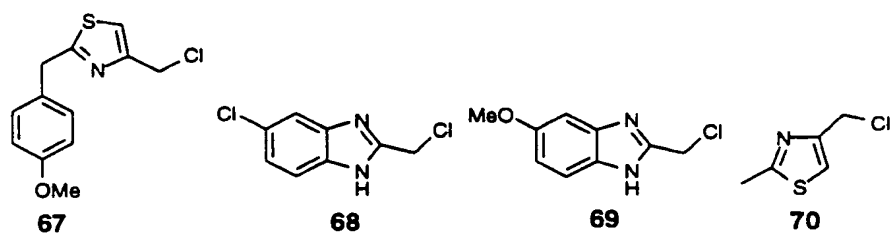
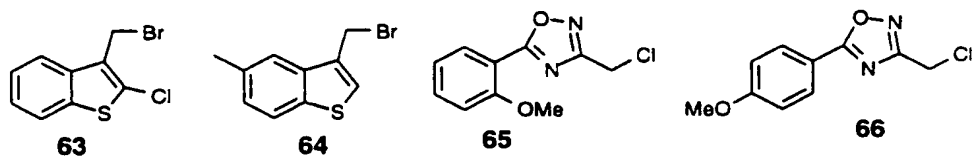
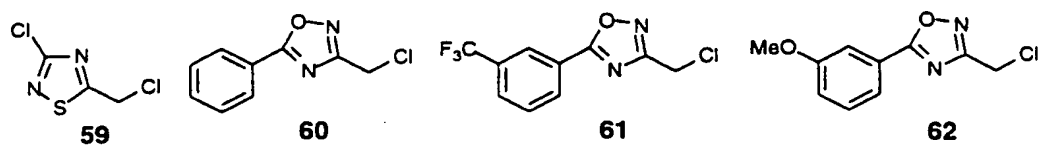
3400



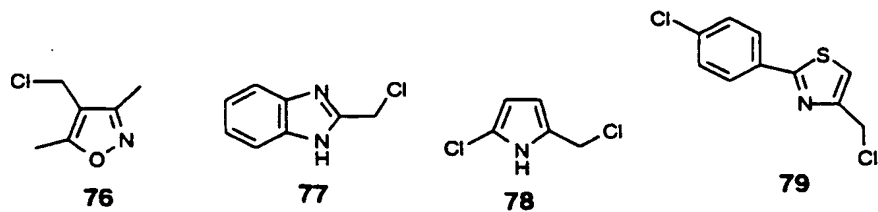
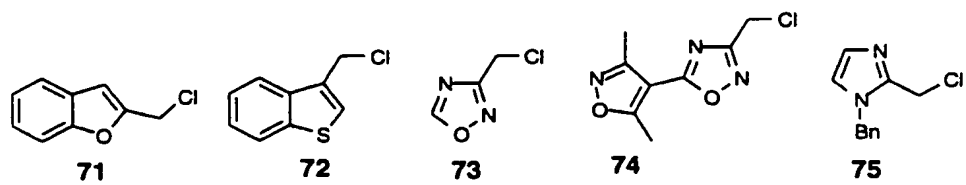
3405

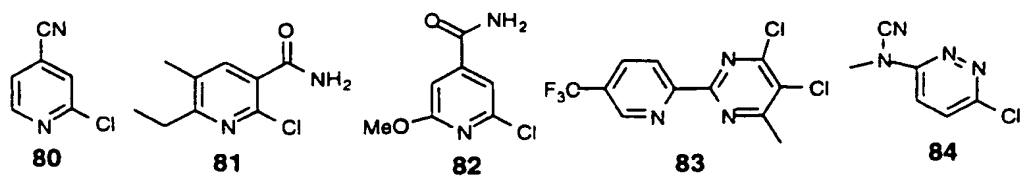


3410

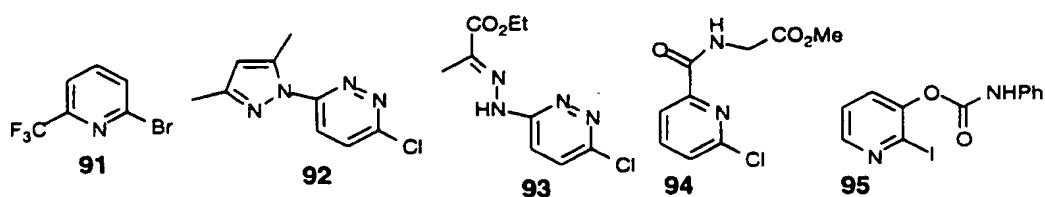
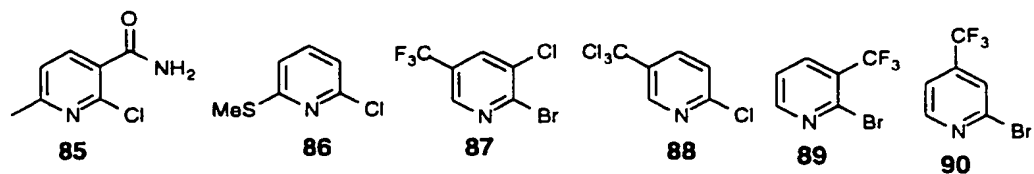


3415

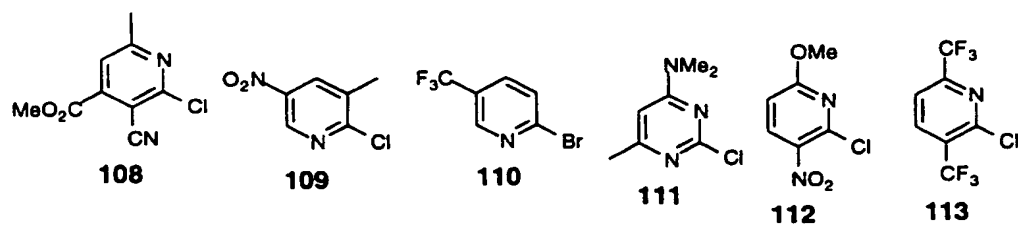
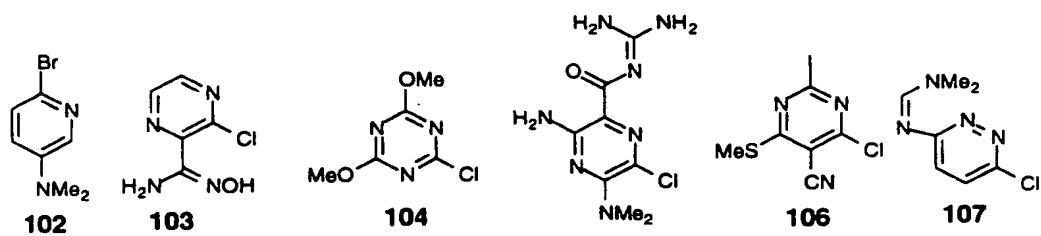
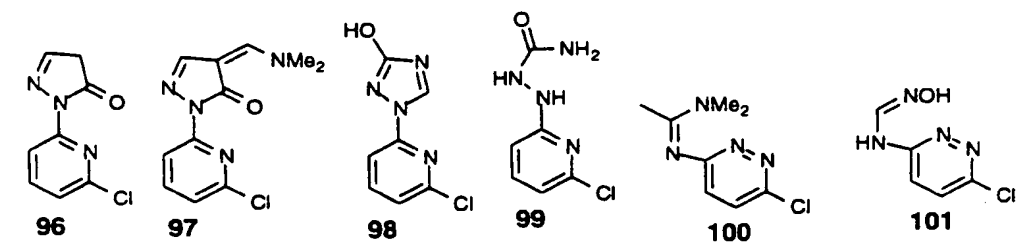




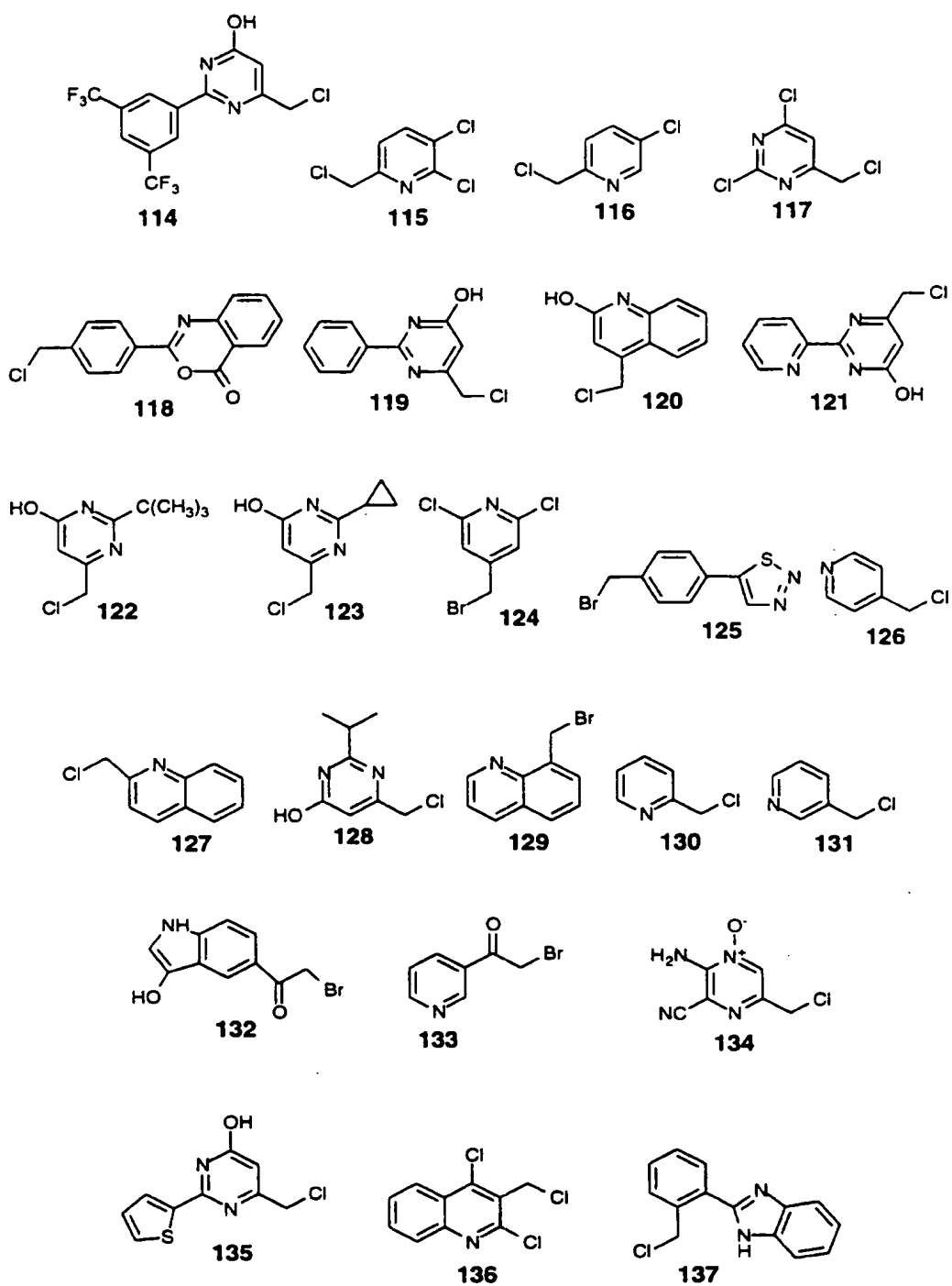
3420



3425

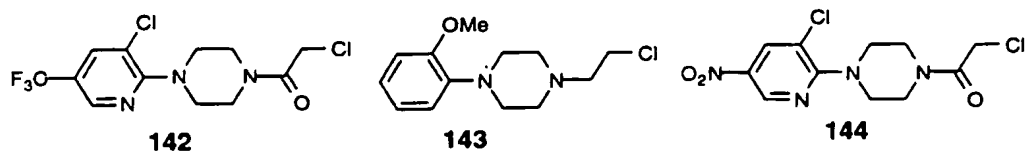
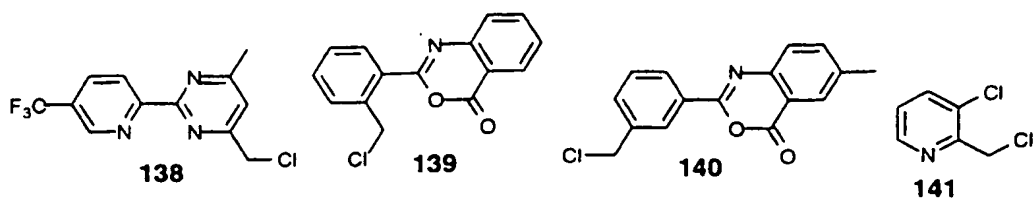


3430

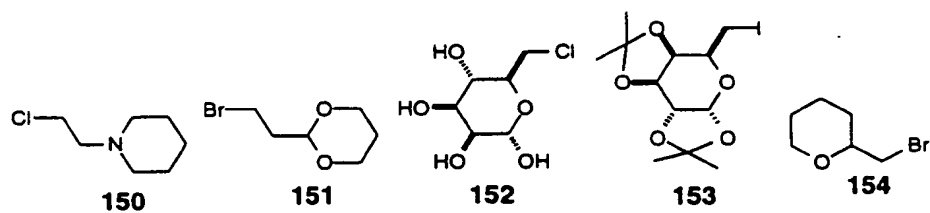
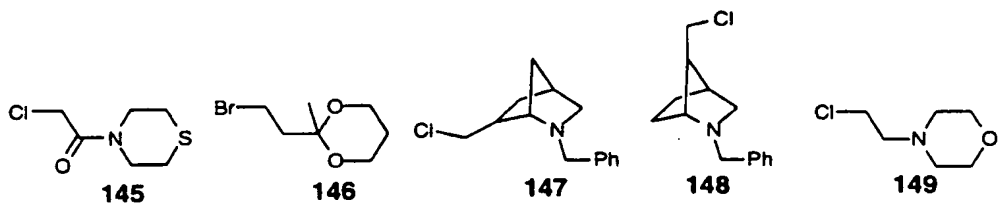


3435

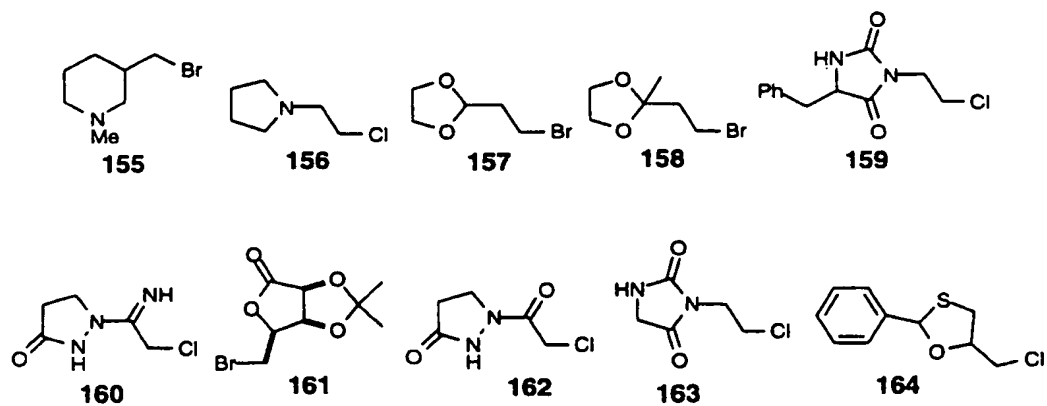
3440

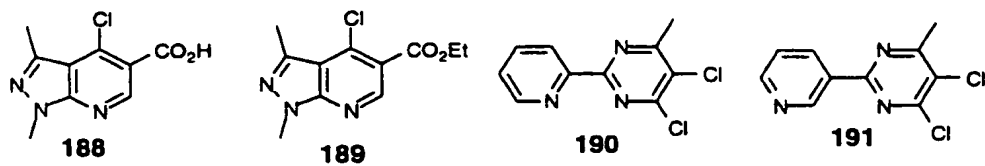
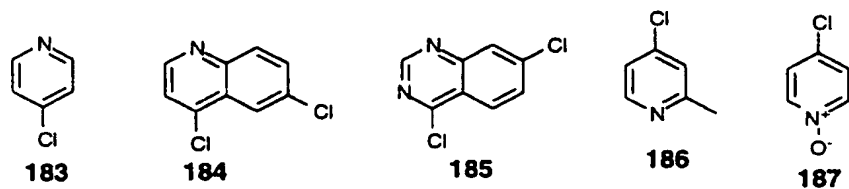
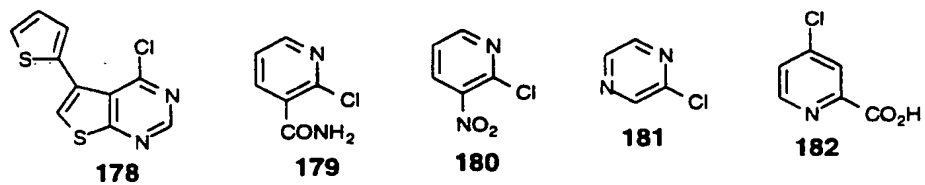
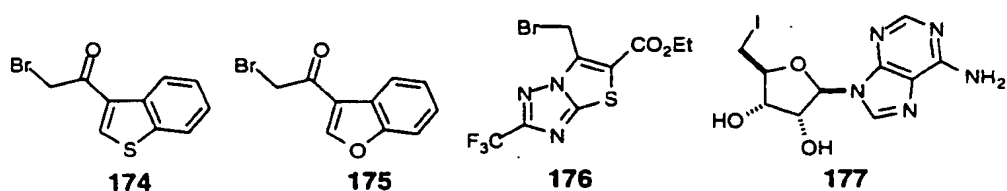
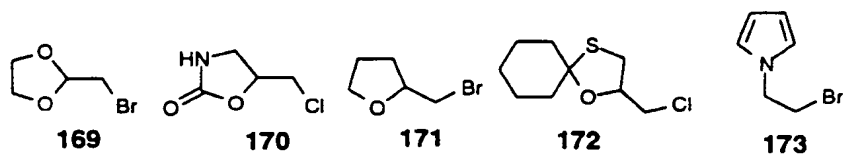
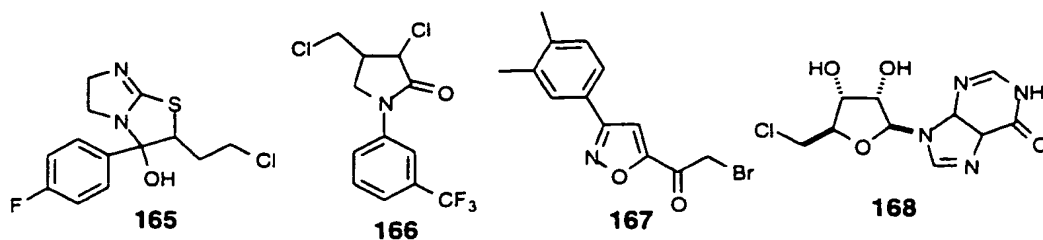


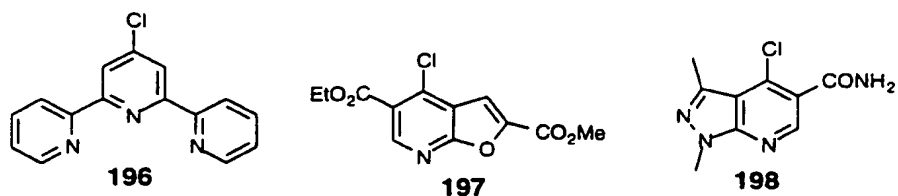
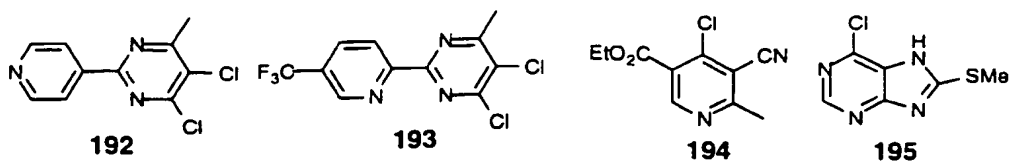
3445



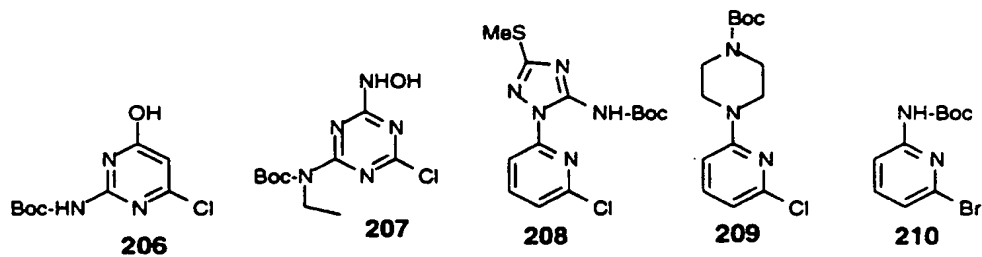
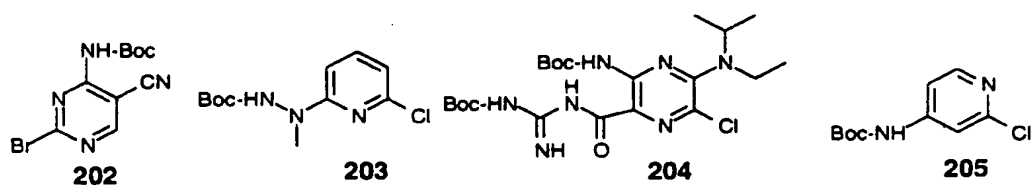
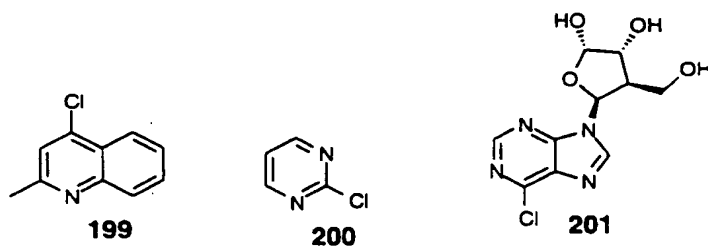
3450



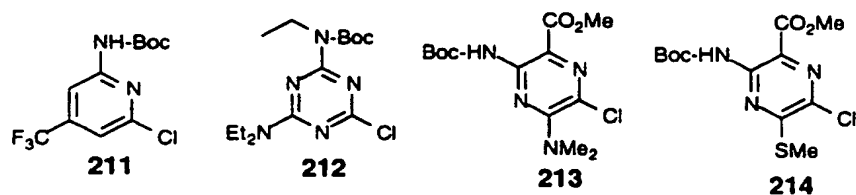


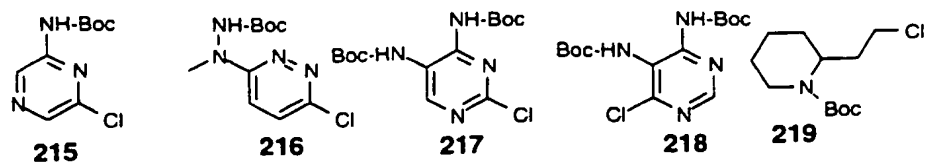


3470

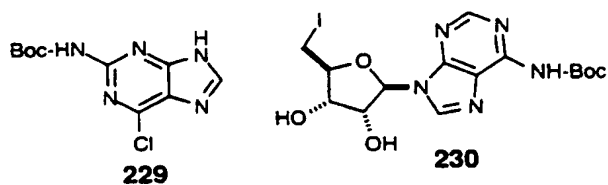
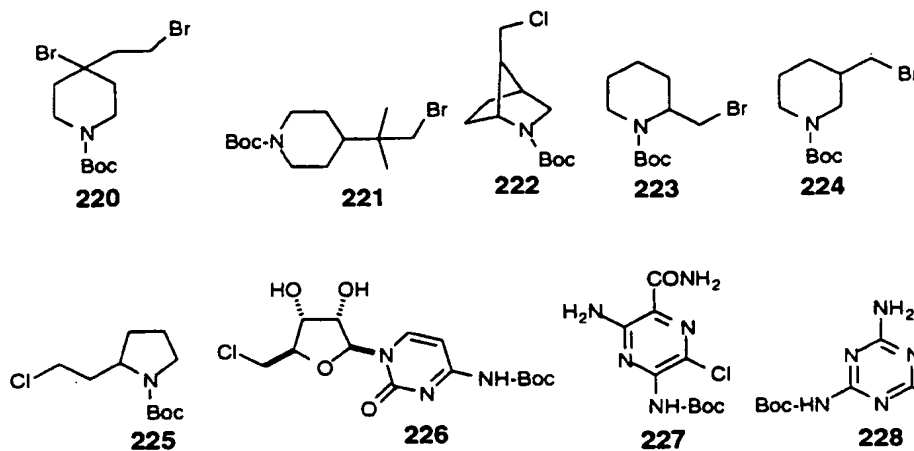


3475

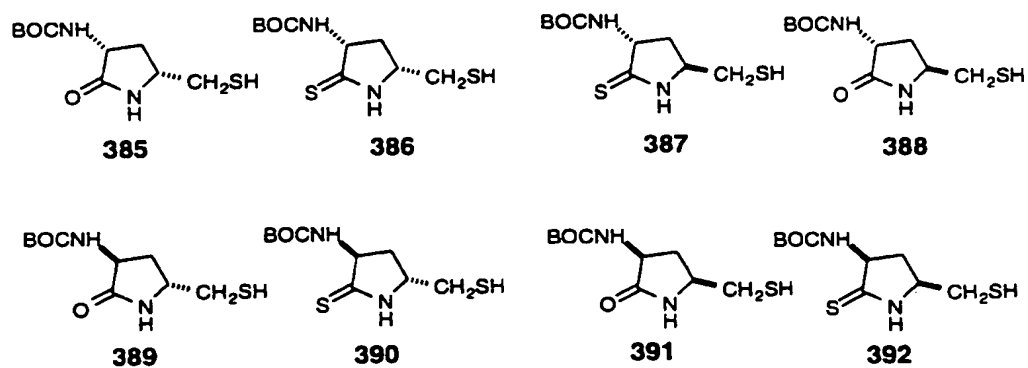




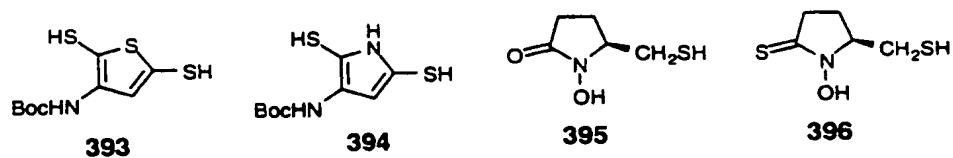
3480

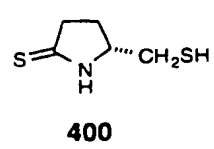
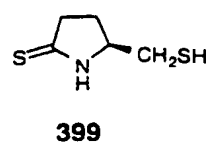
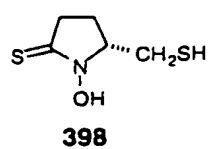
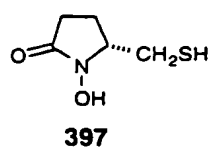


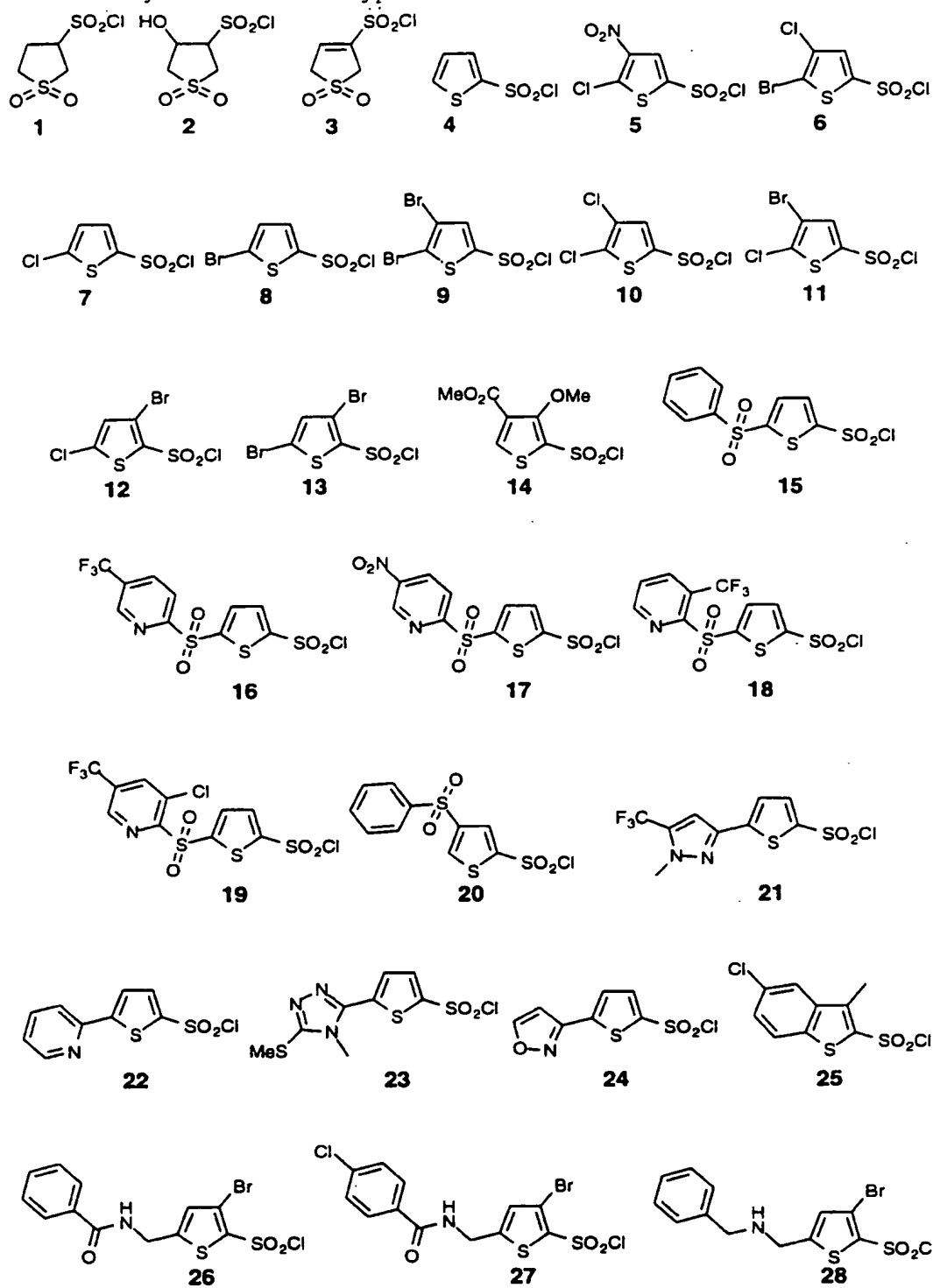
3485

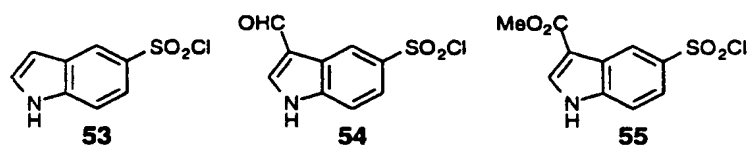
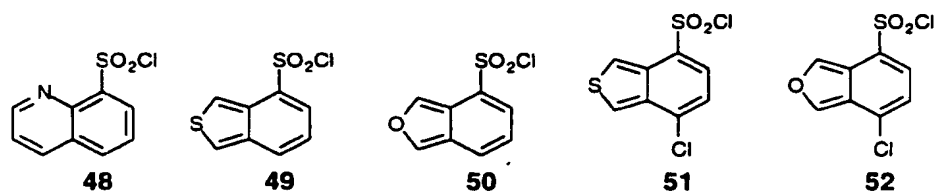
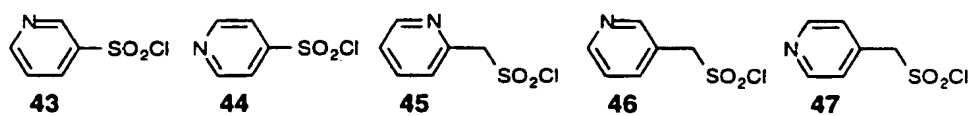
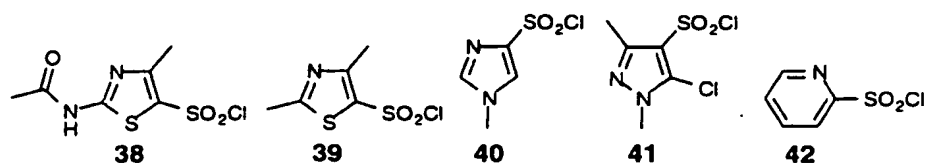
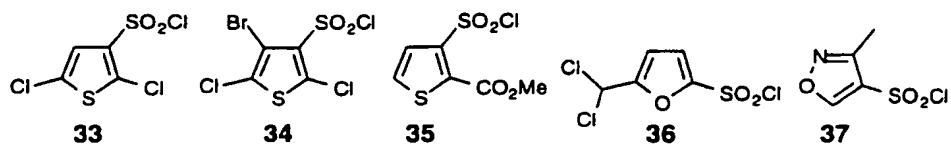
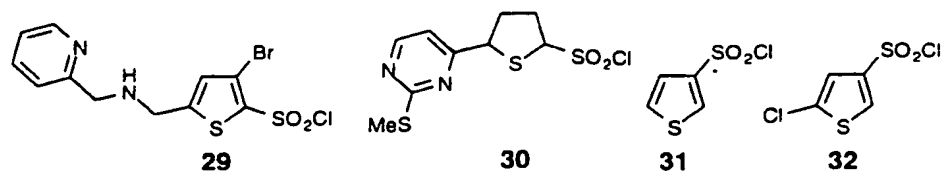


3490





3495 Table 18. Sulfonyl chlorides of the type A-SO₂Cl



The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept.

In Tables 2-10, the abbreviation bz=benzoyl, bn=benzyl, Ph=phenyl, BOC=t-butylloxycarbonyl and TS=p-toluenesulfonyl.

Compound 1

(3-(Aminomethyl)benzoyl)-Met-OCH₃

Step A

(3-(Chloromethyl)benzoyl)-Met-OCH₃

To a solution of methionine methyl ester hydrochloride (2.0 g, 10 mmol) and 3-(chloromethyl)benzoyl chloride (2.08 g, 11.0 mmol) in methylene chloride (50 mL) was slowly added triethylamine (3.07 mL, 22.0 mmol) at ice bath temperature for 2 hours. The mixture was washed with 0.5 N HCl (50 mL x 2), brine (50 mL x 2) and water (50 mL x 2) then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to give the desired product (3.03 g) as a white solid: m.p. 82-83°C;

¹H NMR (CDCl₃) δ 7.82 (1H, s), 7.74 (1H, d, J=7.7 Hz), 7.53 (1H, d, J=7.7 Hz), 7.42 (1H, t, J=7.7 Hz), 7.06 (1H, br d, J=7.6 Hz), 4.92 (1H, ddd, J=7.6, 7.1, 5.1 Hz), 4.59

(2H, s), 3.78 (3H, s), 2.58 (2H, t, J=7.1 Hz), 2.26 (1H, sm), 2.15 (1H, m), 2.10 (3H, s); ¹³C NMR (CDCl₃) δ 172.59, 166.54, 138.13, 134.25, 131.95, 129.12, 127.42, 126.97, 52.72, 52.14, 45.55, 31.47, 30.12, 15.55.

Step B

(3-(Azidomethyl)benzoyl)-Met-OCH₃

A suspension of (3-(chloromethyl)benzoyl)-Met-OCH₃ (1.58 g, 5.0 mmol) and sodium azide (1.3 g, 20.0 mmol) in DMSO (40 mL) was stirred at 80°C for 7 hours. The mixture was diluted with methylene chloride (100 mL), washed with brine (70 mL x 2) and water (70 mL x 2), and then dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure to give a yellow residue. Chromatography on silica gel (30% ethyl acetate in hexanes) to provide the desired product (1.45 g) as a colorless solid: m.p. 48-49°C; ¹H NMR (CDCl₃) δ 7.78 (2H, m), 7.49 (2H, m), 6.99 (1H, br d, J=7.4 Hz), 4.49 (1H, ddd, J=7.4, 7.1, 5.2 Hz), 4.42 (2H, s), 3.80 (3H, s), 2.60 (2H, t, J=7.4 Hz), 2.29 (1H, m), 2.17 (1H, m), 2.12 (3H, s); ¹³C NMR (CDCl₃) δ 177.50, 166.54, 135.97, 134.06,

131.18, 128.89, 126.84, 126.71, 54.09, 52.47, 51.95, 31.38, 30.00, 15.30.

Step C

(3-(Aminomethyl)benzoyl)-Met-OCH₃

A suspension of (3-(azidomethyl)benzoyl)-Met-OCH₃ (1.29 g, 4.0 mmol) and 5%
3560 palladium on carbon (0.2 g) in methanol (40 mL) was stirred under a hydrogen atmosphere
(1 atm) for two days at room temperature. The catalyst was removed by filtration through
celite (1.5 g) and the solvent was evaporated in vacuo. The residue was washed with water
(5 mL x 2) and dried to give the desired product (1.12 g) as a colorless foam. ¹H NMR
(CDCl₃) δ 7.81 (1H, s), 7.68 (1H, d, J=7.4 Hz), 7.45 (1H, d, J=6.5 Hz), 7.36 (1H, t,
3565 J=7.4 Hz), 4.91 (1H, ddd, J=7.3, 7.1, 5.1 Hz), 3.90 (2H, s), 3.77 (3H, s), 3.21 (2H, br
s), 2.59 (2H, t, J=7.4 Hz), 2.20 (1H, m), 2.12 (1H, m), 2.09 (3H, s).

Compound 2(4-(Aminomethyl)benzoyl)-Met-OCH₃

3570 The title compound is prepared according to the procedure used to prepare Compound 1 but
replacing 3-(chloromethyl)benzoyl chloride with 4-(chloromethyl)benzoyl chloride.

Compound 3(3-Aminobenzoyl)-Met-OCH₃

3575 The title compound was prepared according to the procedure described in J. Biol. Chem.
269 12410-12413 (1994).

Compound 4(4-Aminobenzoyl)-Met-OCH₃

3580

Step AN-BOC-4-Aminobenzoic acid

4-Aminobenzoic acid (10 g, 72.9 mmol) was placed into a mixture of dioxane (145.8 mL)
and 0.5 M NaOH (145.8 mL). The solution was cooled to 0°C and di-t-butyl dicarbonate
3585 (23.87 g, 109.5 mmol) was added. The reaction mixture was allowed to warm to room
temperature and stirred overnight. The next day, the dioxane was removed, the residue was
made acidic and extracted into ethyl acetate. The ethyl acetate fractions were combined and
washed with 1N HCl to remove any unreacted starting material. The solution was dried
over Na₂SO₄ and the solvent was removed in vacuo. The crude material was recrystallized
3590 from ethyl acetate/hexanes to provide the desired product (12.2 g): m.p. 189-190°C; ¹H
NMR (CD₃OD) δ 1.52 (9H, s), 7.49 (2H, d, J=8.6 Hz), 7.91 (2H, d, J=8.6 Hz), 9.28
(1H, s); ¹³C NMR (CD₃OD) δ 28.59, 81.29, 118.54, 125.30, 131.81, 145.70, 155.00,
169.80; Anal. Calc. for C₁₂H₁₅NO₄, C: 60.76, H: 6.37, N: 5.90; Found, C: 60.52, H:
6.43, N: 5.83; HRMS Calc. for C₁₂H₁₅NO₄, 237.0961, Found, 237.1001.

3595

Step B(N-BOC-4-Aminobenzoyl)-Met-OCH₃

Into a dried, nitrogen filled flask was placed N-BOC-4-aminobenzoic acid (8.77 g, 36.97 mmol) in dry methylene chloride (148 mL) along with methionine methyl ester
3600 hydrochloride (8.12 g, 40.66 mmol). This solution was cooled in an ice bath and triethylamine (6.7 mL), EDCI (7.80 g, 40.66 mmol) and hydroxybenzotriazole (HOBT, 5.50 g, 40.66 mmol) were added. The mixture was stirred overnight, diluted with more methylene chloride and was extracted three times each with 1 M HCl, 1M NaHCO₃ and water. The methylene chloride was dried over MgSO₄ and the solvent was removed in
3605 vacuo. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (9.72 g): m.p. 184-185°C; ¹H NMR (CDCl₃) δ 1.53 (9H, s), 2.06-2.18 (4H, m), 2.23-2.33 (1H, m), 2.59 (2H, t, J=7.6 Hz), 3.80 (3H, s), 4.92 (1H, m), 7.45 (2H, d, J=8.7 Hz), 7.77 (2H, d, J=8.7 Hz); ¹³C NMR (CDCl₃) δ 15.59, 28.34, 30.15, 31.64, 52.10, 52.73, 81.20, 117.73, 127.8, 128.33, 141.88, 152.33, 166.50, 172.75;
3610 Anal. Calc. for C₁₈H₂₆N₂O₅S, C: 56.53, H: 6.85, N: 7.29; Found, C: 56.47, H: 6.86, N: 7.29; m/z (EI) 382 (M).

Step C(4-Aminobenzoyl)-Met-OCH₃ hydrochloride

3615 N-BOC-4-aminobenzoyl-Met-OCH₃ (3.53 g, 9.59 mmol) was placed into methylene chloride (30-35 mL) and to it was added 3M HCl/EtO₂ (38.4 mL). After standing, a white precipitate formed. After two hours the solution was decanted and the crystals were collected by centrifugation. The crystals were then washed several times with fresh ether and dried overnight on the vacuum pump. Meanwhile, the filtrate was left to stand
3620 overnight to allow additional product to precipitate. The second fraction was washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 2.87 g: m.p. 158-164°C; ¹H NMR (CDCl₃) δ 2.10 (3H, s), 2.12-2.29 (1H, m), 2.52-2.71 (1H, m), 2.59 (2H, t, J=7.6 Hz), 3.75 (3H, s), 4.79 (1H, m), 7.02 (2H, d, J=8.6 Hz), 7.55 (2H, d, J=8.6 Hz); ¹³C NMR (CDCl₃) δ 15.23, 31.43, 31.53, 52.91, 52.43, 124.35, 130.56, 135.31, 135.76, 168.95, 173.87; HRMS Calc. for C₁₃H₁₈N₂O₃S, 282.1038, Found 282.1009.

Compound 5(4-Amino-3-methylbenzoyl)-Met-OCH₃

3630

Step A

N-BOC-4-Amino-3-methylbenzoic acid

4-Amino-3-methylbenzoic acid (5 g, 33.1 mmol) was reacted according to the same procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The resulting orange-brown solid was recrystallized from ethyl acetate and hexanes to provide the desired product (4.99 g) as tan prismatic crystals: m.p. 180-182°C; ¹H NMR (CD₃OD) δ 1.51 (9h, s), 2.27 (3H, s), 7.66 (1H, d, *J*=8.1 Hz), 7.79-7.82 (2H, m), 8.32 (1H, s); ¹³C NMR (CD₃OD) δ 17.98, 28.62, 81.47, 123.12, 127.05, 129.14, 130.65, 132.99, 142.45, 155.33, 168.70; Anal. Calc. for C₁₃H₁₇NO₄, C: 62.15, H: 6.82, N: 5.58; Found C: 62.07, H: 6.86, N: 5.46; *m/z* (EI) 251; HRMS Calc. for C₁₃H₁₇NO₄, 251.1158; Found, 251.1153.

Step B(N-BOC-4-Amino-3-methylbenzoyl)-Met-OCH₃

N-BOC-4-amino-3-methylbenzoic acid (2.00 g, 7.96 mmol) was reacted with with methionine methyl ester hydrochloride (1.75 g, 8.76 mmol), triethylamine (1.4 mL), EDCI (1.68 g, 8.76 mmol) and hydroxybenzotriazole (HOBT, 1.18 g, 8.76 mmol) in dry methylene chloride (31.8 mL) according to the procedure described for the preparation of N-BOC-4-aminobenzoyl)-Met-OCH₃. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (2.61 g): m.p. 163-165°C; ¹H NMR (CDCl₃) δ 1.54 (9H, s), 2.06-2.18 (4H, m), 2.23-2.34 (4H, m), 2.59 (2H, t, *J*=6.8 Hz), 3.80 (3H, s), 4.92 (1H, m), 6.45 (1H, s), 6.88 (1H, d, *J*=7.5 Hz), 7.63 (1H, d, *J*=8.6 Hz), 7.66 (1H, s), 8.05 (1H, d, *J*=8.6 Hz); ¹³C NMR (CDCl₃) δ 15.47, 17.61, 28.22, 30.03, 31.55, 51.93, 52.57, 81.04, 118.73, 125.62, 127.66, 129.54, 139.89, 152.34, 166.58, 172.66.

Step C(4-Amino-3-methylbenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-Amino-3-methylbenzoyl-Met-OCH₃ (0.99 g, 2.59 mmol) was dissolved in methylene chloride (15-20 mL) and precipitated with 3M HCl/Et₂O (20.7 mL). A pale orange precipitate was obtained, washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 0.83 g: m.p. 157-159°C; ¹H NMR (CD₃OD) δ 2.04 (3H, s), 2.11-2.25 (1H, m), 2.47 (3H, s), 2.52-2.68 (3H, m), 3.74 (3H, s), 4.75-4.80 (1H, m), 7.48 (1H, d, *J*=8.2 Hz), 7.81 (2H, d, *J*=8.2 Hz), 7.87 (1H, s); ¹³C NMR (CD₃OD) δ 15.23, 17.28, 31.43, 31.51, 52.91, 53.37, 124.41, 127.85, 131.99, 133.63, 134.14, 135.65, 169.05, 173.84; Anal. Calc. for C₁₄H₂₁N₂O₃S, C: 50.52, H: 6.36, N: 8.42; Found C: 50.71, H: 6.40, N: 8.34.

Compound 6(4-Amino-3-methoxybenzoyl)-Met-OCH₃Step AN-BOC-4-Amino-3-methoxybenzoic acid

4-Amino-3-methoxybenzoic acid (1 g, 5.98 mmol) was reacted according to the same
3675 procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The
resulting solid was recrystallized from ethyl acetate and hexanes to provide the desired
product (1.5 g) as tan crystals: m.p. 176-178°C; ¹H NMR (CD₃OD) δ 1.52 (9H, s), 3.92
(3H, s), 7.56 (1H, s), 7.62 (1H, d, J=8.4 Hz), 7.96 (1H, s), 8.03 (1H, d, J=8.4 Hz); ¹³C
NMR (CD₃OD) δ 28.53, 56.35, 81.78, 112.01, 118.58, 124.20, 125.76, 133.84,
3680 149.04, 154.20, 169.60; HRMS Calc. for C₁₃H₁₇NO₅, 267.1107; Found, 267.1103.

Step B(N-BOC-4-Amino-3-methoxybenzoyl)-Met-OCH₃

N-BOC-4-amino-3-methoxybenzoic acid (0.35 g, 1.31 mmol) was reacted with with
3685 methionine methyl ester hydrochloride (0.9 g, 1.43 mmol) using EDCI according to the
procedure described for the preparation of (N-BOC-4-aminobenzoyl)-Met-OCH₃.

The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired
product (0.36 g): m.p. 163-165°C; ¹H NMR (CDCl₃) δ 1.53 (9H, s), 2.09-2.18 (4H, m),
2.23-2.35 (1H, m), 2.60 (2H, t, J=6.9 Hz), 3.80 (3H, s), 3.93 (3H, s), 4.92 (1H, br s),
3690 6.93 (1H, d, J=7.6 Hz), 7.25 (1H, m), 7.31 (1H, d, J=10.2 Hz), 7.44 (1H, s), 8.15 (1H,
d, J=8.5 Hz); ¹³C NMR (CDCl₃) δ 15.47, 28.23, 30.09, 31.48, 52.06, 52.54, 55.81,
80.82, 98.06, 109.38, 116.66, 119.31, 131.52, 147.23, 152.31, 166.57, 172.58; m/z
(FAB) 413 (M + 1).

Step C(4-Amino-3-methoxybenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-Amino-3-methoxybenzoyl-Met-OCH₃ (0.71 g, 1.79 mmol) was dissolved in
methylene chloride (4 mL) and precipitated with 3M HCl/Et₂O (12 mL). A reddish
precipitate was obtained, washed with ether and dried overnight on the vacuum pump. The
3700 total yield of the desired product was 0.55 g: m.p. 176-177°C; ¹H NMR (CD₃OD) δ 2.08
(3H, s), 2.21 (2H, m), 2.61 (2H, m), 3.74 (3H, s), 4.02 (3H, s), 4.79 (1H, m), 7.50
(1H, d, J=8.2 Hz), 7.57 (1H, d, J=4.1 Hz), 7.67 (1H, s); ¹³C NMR (CD₃OD) δ 15.26,
31.34, 31.42, 52.95, 53.38, 57.12, 112.29, 121.43, 124.57, 124.77, 136.15, 153.67,
168.79, 173.81.

Compound 7
(4-Amino-1-naphthoyl)-Met-OCH₃

Step A

3710 4-Amino-1-naphthoic acid
4-Amino-1-naphthalenecarbonitrile (1.5 g, 8.91 mmol) was suspended in a 50% KOH solution (18 mL). The heterogeneous solution was heated at reflux for 2-3 days. Once the solution became homogeneous and TLC showed no more starting material, the deep red solution was cooled and poured over 200 mL of water. The resulting solution was then
3715 filtered and the desired product was precipitated with concentrated HCl. The resulting red crystals were filtered and the filtrate was refiltered to give pink crystals. The first fraction of crystals was treated with activated carbon to remove some of the red color. A total of 1.51 g of the desired product was obtained: m.p. 169-171°C; ¹H NMR (CD₃OD) δ 6.69 (1H, d, J=8.2 Hz), 7.38-7.43 (1H, m), 7.48-7.54 (1H, m), 8.03 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.2 Hz), 9.09 (1H, d, J=8.5 Hz); ¹³C NMR (CD₃OD) δ 107.39, 114.61, 122.99,
3720 123.92, 125.21, 127.40, 128.48, 135.04, 151.35, 171.44; HRMS Calc. for C₁₁H₇NO₂, 187.0633; Found, 187.0642.

Step B

3725 N-BOC-4-Amino-1-naphthoic acid
4-Amino-1-naphthoic acid (0.86 g, 4.61 mmol) was dissolved in dioxane (9.2 mL). Di-*t*-butyl dicarbonate (1.11 g, 5.07 mmol) was added and the mixture was stirred overnight. The reaction mixture was worked up as described above for N-BOC-4-aminobenzoic acid to give 0.76 g of the desired product as a reddish pink solid: m.p. 194-195°C; ¹H NMR (CD₃OD) δ 1.56 (9H, s), 7.53-7.62 (2H, m), 7.79 (1H, d, J=8.1 Hz), 8.12 (1H, d, J=8.0 Hz), 8.22 (1H, d, J=8.18 Hz), 9.02 (1H, d, J=8.9 Hz); ¹³C NMR (CD₃OD) δ 26.68,
3730 81.62, 119.06, 123.40, 124.57, 127.03, 127.37, 128.49, 128.77, 131.89, 133.76, 139.86, 155.95, 170.73; Anal. Calc. for C₁₇H₁₇NO₄, C: 66.90, H: 5.96, N: 4.88; Found C: 66.49, H: 6.08, N: 4.79; m/z (EI), 289; HRMS Calc. for C₁₆H₁₇NO₄, 287.1158;
3735 Found, 287.1151.

Step C

(N-BOC-4-Amino-1-naphthoyl)-Met-OCH₃

N-BOC-4-Amino-naphthoic acid (0.46 g, 1.60 mmol), methionine methyl ester
3740 hydrochloride (0.35 g, 1.76 mmol), EDCI (0.43 g, 1.76 mmol), HOBT (0.24 g, 1.76 mmol) and triethylamine (0.27 mL) in methylene chloride (6.4 mL) were reacted as described above for N-BOC-4-aminobenzoyl-Met-OCH₃. After workup and

recrystallization from ethyl acetate hexanes, the desired product (0.44 g) was obtained as pale pink crystals: m.p. 131-132°C; ¹H NMR (CDCl₃) δ 1.57 (9H, s), 2.11-2.21 (4H, m), 2.29-2.41 (1H, m), 2.65 (2H, t, *J*=7.1 Hz), 3.83 (3H, s), 4.99-5.06 (1H, m), 6.68 (1H, d, *J*=8.0 Hz), 7.02 (1H, s), 7.56-7.59 (2H, m), 7.69 (1H, d, *J*=7.9 Hz), 7.87-7.90 (1H, m), 8.02 (1H, d, *J*=7.9 Hz), 8.44-8.48 (1H, m); ¹³C NMR (CDCl₃) δ 15.56, 28.31, 30.19, 31.65, 52.06, 52.64, 81.17, 115.82, 120.18, 125.79, 126.37, 126.53, 127.18, 131.02, 135.65, 152.93, 169.04, 172.40; HRMS Calc. for C₂₂H₂₈N₂O₅S, 432.1719; Found, 432.1702; *m/z* (FAB) 433 (*M*+1).

Step D

(4-Amino-1-naphthoyl)-Met-OCH₃ hydrochloride

(*N*-BOC-4-Amino-1-naphthoyl)-Met-OCH₃ (0.57 g, 1.31 mmol) was deprotected with HCl/ether to yield the desired product (0.31 g) as a white solid: m.p. 178-181°C; ¹H NMR (CD₃OD) δ 2.08-2.16 (4H, m), 2.20-2.30 (1H, m), 2.57-2.75 (2H, m), 3.82 (3H, s), 4.87-4.91 (1H, m), 7.59 (1H, d, *J*=7.5 Hz), 7.67 (1H, d, *J*=7.5 Hz), 7.71-7.80 (2H, m), 8.03 (1H, dd, *J*=7.1, 2.0 Hz), 8.35 (1H, dd, *J*=6.8, 1.8 Hz); ¹³C NMR (CD₃OD) δ 15.23, 31.40, 53.01, 53.33, 119.90, 122.20, 126.15, 127.41, 127.77, 129.09, 129.31, 131.50, 132.33, 135.64, 171.77, 173.83; *m/z* (FAB), 369 (*M*+1).

Compound 8

(4-Amino-2-phenylbenzoyl)-Met-OCH₃

Step A

4-Nitro-2-phenyltoluene

2-Bromo-4-nitrotoluene (2.16 g, 10.00 mmol) and phenylboric acid (1.46 g, 12.00 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added Pd(Ph₃P)₄ (0.58 g, 5%). The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et₂O. The crude product was chromatographed on silica gel using hexanes as eluent. After recrystallization from ethanol, the desired product (1.23 g) was obtained as pale orange needles: m.p. 69-71°C; ¹H NMR (CDCl₃) δ 2.36 (3H, s), 7.29-7.40 (2H, m), 7.41-7.49 (5H, m), 8.07-8.10 (2H, m); ¹³C NMR (CDCl₃) δ 20.68, 121.96, 124.51, 127.78, 128.41, 128.83, 131.06, 139.06, 139.44, 142.97, 143.48, 146.05; Anal. Calc. for C₁₃H₁₁NO₂, C: 73.26, H: 5.20, N: 6.57; Found, C: 73.10, H: 5.12, N: 6.50; *m/z* (EI) 213; HRMS Calc. for C₁₃H₁₁NO₂, 213.0790; Found, 213.0793.

Step B

3780

4-Nitro-2-phenylbenzoic acid

3785

4-Nitro-2-phenyltoluene (0.5 g, 2.34 mmol) was dissolved in water (4.6 mL) and pyridine (2.3 mL). The mixture was heated to reflux and KMnO_4 (1.85 g, 11.7 mmol) was added. The reaction mixture was heated overnight and the solution was filtered and washed several times with boiling water. The aqueous solution was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solution was dried over Na_2SO_4 and the solvent removed in vacuo to provide the desired product (0.37 g): m.p. 174-176°C, ^1H NMR (CD_3OD) δ 7.38-7.48 (5H, m), 7.96 (1H, d, $J=8.5$ Hz), 8.21 (1H, d, $J=2.3$ Hz), 8.28 (1H, dd, $J=8.48, 2.37$ Hz); ^{13}C NMR (CD_3OD) δ 122.95, 126.09, 129.27, 129.42, 129.49, 131.56, 139.26, 140.42, 144.41, 150.17, 170.52; m/z (EI) 243 (M).

3790

Step C(4-Nitro-2-phenylbenzoyl)-Met-OCH₃

3795

4-Nitro-2-phenylbenzoic acid (0.3 g, 1.23 mmol), methionine methyl ester hydrochloride salt (0.27 g, 1.35 mmol), EDCI (0.26 g, 1.35 mmol), HOBT (0.18 g, 1.35 mmol) and triethylamine (0.19 mL) in dry methylene chloride (4.9 mL) were reacted according the procedure described above for (N-BOC-4-aminobenzoyl)-Met-OCH₃. After recrystallization of the product from ethyl acetate hexanes, the desired product (0.41 g) was obtained: m.p. 98-101°C; ^1H NMR (CDCl_3) δ 1.62-1.73 (1H, m), 1.79-1.88 (1H, m), 1.91 (3H, s), 1.99 (2H, t, $J=7.2$ Hz), 3.59 (3H, s), 4.53 (1H, m), 6.45 (1H, d, $J=7.8$ Hz), 7.33-7.40 (5H, m), 7.67 (1H, d, $J=8.3$ Hz), 8.07-8.12 (2H, m); ^{13}C NMR (CDCl_3) δ 14.92, 29.11, 30.67, 51.51, 52.29, 121.86, 124.74, 128.27, 128.60, 128.69, 129.52, 137.50, 140.56, 141.02, 148.09, 167.23, 171.23; m/z (FAB), 389 (M+1).

3800

Step D(4-Amino-2-phenylbenzoyl)-Met-OCH₃

3805

(4-Nitro-2-phenylbenzoyl)-Met-OCH₃ (0.35 g, 0.90 mmol) was dissolved in ethyl acetate (9.0 mL). To this mixture was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1.02 g, 4.5 mmol) and the reaction mixture was heated under nitrogen at reflux for one hour. The mixture was poured onto ice, the solution was made basic using NaHCO_3 and the product was extracted into ethyl acetate several times (7-8). The ethyl acetate solutions were combined, washed with brine and dried over Na_2SO_4 . The solvent was removed in vacuo to the desired product (0.24 g) as a yellow solid: ^1H NMR (CDCl_3) δ 1.58-1.70 (1H, m), 1.80-1.92 (1H, m), 1.98 (3H, s), 2.06 (2H, t, $J=7.7$ Hz), 3.62 (3H, s), 4.00 (2H, br s), 4.56-4.63 (1H, m), 5.84 (1H, d, $J=7.7$ Hz), 6.50 (1H, s), 6.61 (1H, d, $J=8.4$ Hz) 7.29-7.42 (5H, m), 7.58 (1H, d, $J=8.3$ Hz); ^{13}C NMR (CDCl_3) δ 15.02, 29.25, 31.25, 51.57, 52.15, 113.27, 115.88, 123.52, 127.56, 128.37, 128.44, 130.92, 140.66, 141.44, 148.53, 168.58, 171.91.

3810

3815

Compound 9(4-Amino-2-(2-thienyl)benzoyl)-Met-OCH₃

3820 The title compound can be prepared according to the method used to prepare Compound 8, only substituting thiophene-2-boronic acid for phenyl boronic acid.

Compound 10(4-Amino-2-(1-naphthyl)benzoyl)-Met-OCH₃

3825 The title compound can be prepared according to the method used to prepare Compound 8, only substituting 1-naphthylboronic acid for phenylboronic acid.

Compound 114-Amino-3'-methylbiphenyl

3830 The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Compound 124-Amino-4'-biphenyl carboxylic acid

3835

Step A4-Nitro-4'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-4-methylbenzene.

3840

Step B4-Nitro-4'-biphenyl carboxylic acid

The title compound was prepared by KMnO₄ oxidation of 4-nitro-4'-methylbiphenyl.

3845

Step C4-Amino-4'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-4'-biphenyl carboxylic acid.

3850

Compound 134-Amino-3'-biphenyl carboxylic acidStep A

4-Nitro-3'-methylbiphenyl

3855 The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Step B4-Nitro-3'-biphenyl carboxylic acid

3860 The title compound was prepared by KMnO_4 oxidation of 4-nitro-3'-methylbiphenyl.

Step C4-Amino-3'-biphenyl carboxylic acid

3865 The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-3'-biphenyl carboxylic acid.

Compound 144-Amino-2-methoxy-3'-biphenyl carboxylic acid

3870 Step A

2-Methoxy-4-nitro-3'-methylbiphenyl

The title compound was prepared by reaction of 1-bromo-2-methoxy-4-nitrobenzene with 3-methylphenylboronic acid in the presence of palladium acetate.

3875 Step B

2-Methoxy-4-nitro-3'-biphenylcarboxylic acid

The title compound was prepared by KMnO_4 oxidation of 2-methoxy-4-nitro-3'-methylbiphenyl.

3880 Step C

4-Amino-2-methoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 2-methoxy-4-nitro-3'-biphenyl carboxylic acid.

3885 Compound 15

4-Amino-2-isopropoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

3890 Compound 16

4-Amino-2-phenyl-3'-biphenylcarboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

Compound 17(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃Step A2-Bromo-4-nitrobenzoic acid

3895 2-Bromo-4-nitrotoluene (5.0 g, 23.14 mmol) was dissolved in pyridine (23 mL) and water (46 mL). The heterogeneous mixture was heated to 60°C and KMnO₄ (18.29 g, 115.7 mmol) was added carefully. The mixture was then heated under reflux overnight. The reaction mixture was filtered and washed with boiling water. The solution was then made acidic and extracted into ethyl acetate, dried over Na₂SO₄ and the solvent was removed in
3905 vacuo. The crude product was dissolved in aqueous NaOH and washed with hexanes. The aqueous phase was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solutions were combined and dried over Na₂SO₄ and the solvent was removed in vacuo to provide the desired product (3.72 g): m.p. 158-160°C; ¹H NMR (CD₃OD) δ 7.81 (1H, d, J=8.5 Hz), 8.08 (1H, d, J=8.5 Hz), 8.30 (1H, s); ¹³C NMR (CD₃OD) δ
3910 121.96, 122.75, 129.36, 132.24, 139.52, 149.54, 167.75; Anal. Calc. for C₇H₄BrNO₄ •0.1 ethyl acetate, C: 34.88, H: 1.90, N: 5.50; Found, C: 34.68, H: 1.86, N: 5.82.

Step B3,5-Dimethylphenylboronic acid

3915 Magnesium turnings (1.44 g, 59.43 mmol) were covered with dry THF (18.8 mL) in a dried, nitrogen filled flask fitted with an addition funnel and reflux condenser. To this was added 5-bromo-m-xylene (10 g, 54.03 mmol) in THF (15 mL) after initiation of the Grignard reaction. The addition was carried out over several minutes and the reaction mixture was heated at reflux for 1-2 hours until most of the magnesium had reacted. The
3920 reaction mixture was then cooled and transferred to an addition funnel fitted to a nitrogen filled flask containing triisopropyl borate (24.9 mL) at -70°C. The dropwise addition was carried out over several minutes and the mixture warmed to room temperature and stirred overnight. The grey solution was poured onto 2 M HCl and immediately turned yellow. The solution was extracted with Et₂O and the Et₂O fractions were combined, dried over
3925 MgSO₄ and the solvent was removed in vacuo to provide the desired product (2.41 g): m.p. 249-251°C; ¹H NMR (CDCl₃) δ 2.44 (6H, s), 7.23 (1H, s), 7.84 (2H, s); ¹³C NMR (CD₃OD) δ 21.36, 133.28, 134.39, 137.48.

Step C4-Nitro-2-(3,5-dimethylphenyl)benzoic acid

2-Bromo-4-nitrobenzoic acid (0.43 g, 2.03 mmol) and 3,5-dimethylphenyl boronic acid (0.334 g, 2.23 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added Cs_2CO_3 (1.66 g, 5.08 mmol) followed by $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.12 g, 5%).

The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et_2O . It was dried over MgSO_4 and the solvent was removed in vacuo. The crude product was chromatographed on silica gel using a 9:1 mixture of hexanes and ethyl acetate to provide the desired product (0.34 g): ^1H NMR (CDCl_3) δ 2.36 (6H, s), 6.99 (2H, s), 7.07 (1H, s), 8.03 (1H, d, $J=9.0$ Hz), 8.23-8.25 (2H, m); ^{13}C NMR (CDCl_3) δ 21.28, 121.68, 123.68, 125.74, 126.07, 130.22, 131.19, 131.31, 135.04, 138.21, 144.74, 170.75.

Step D(4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃

4-Nitro-2-(3,5-dimethylphenyl)benzoic acid (0.15 g, 0.55 mmol), methionine methyl ester hydrochloride (0.11 g, 0.55 mmol), EDCI (0.11 g, 0.55 mmol), HOBT (0.07 g, 0.55 mmol) and triethylamine (0.08 mL) in dry methylene chloride (2.2 mL) were reacted and worked up according to the procedure for (N-BOC-4-aminobenzoyl)-Met-OCH₃ as described above. After recrystallization from ethyl acetate and hexanes, the desired product was obtained (0.13 g): m.p. 122-124°C; ^1H NMR (CDCl_3) δ 1.2-1.84 (1H, m), 1.85-1.97 (1H, m), 2.01 (3H, s), 2.05 (3H, t, $J=7.7$ Hz), 2.38 (6H, s), 3.70 (3H, s), 4.67-4.74 (1H, m), 6.03 (1H, d, $J=7.9$ Hz), 7.05 (2H, s), 7.09 (1H, s), 7.84-7.87 (1H, m), 7.84-7.87 (1H, m), 8.23-8.26 (2H, m); ^{13}C NMR (CDCl_3) δ 15.20, 21.26, 29.22, 31.15, 51.79, 52.57, 122.07, 125.11, 126.27, 130.03, 130.53, 137.77, 138.82, 140.29, 141.56, 148.41, 167.14, 171.53.

Step E(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃

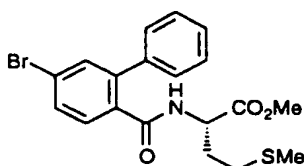
(4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃ (0.11 g, 0.26 mmol) was dissolved in ethyl acetate (3.0 mL). To this mixture was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.3 g, 1.30 mmol) and the reaction was heated under nitrogen at reflux for 6 hours. The mixture was worked up as described above for (4-amino-2-phenylbenzoyl)-Met-OCH₃ to give the desired product (0.15 g): ^1H NMR (CDCl_3) δ 1.60-1.70 (1H, m), 1.80-1.90 (1H, m), 1.99 (3H, s), 2.05 (2H, t, $J=7.6$ Hz), 2.33 (6H, s), 3.64 (3H, s), 3.93 (2H, br s), 4.61-4.64 (1H, m), 5.82 (1H, d, $J=7.7$ Hz), 6.49 (1H, d, $J=2.3$ Hz), 6.62 (1H, dd, $J=8.4, 2.4$ Hz), 6.98 (2H, s),

3965 7.00 (1H, s), 7.65 (1H, d, $J=8.3$ Hz); ^{13}C NMR (CDCl_3) δ 15.08, 21.17, 29.28, 31.49, 51.70, 52.18, 113.30, 115.94, 123.55, 126.36, 129.32, 131.23, 138.15, 140.72, 141.92, 148.40, 168.45, 172.01.

Preparation 1

3970 Anilines of the formula B-NH₂

The anilines from Table 1, entries 10-126 (B-NH₂) are prepared using the procedures for Compounds 1-18 with the exception that methionine methyl ester is replaced by methioninesulfone methyl ester, (S-Me)cysteine methyl ester, serine methyl ester, (O-Me)serine methyl ester, (O-Me)homoserine methyl ester, homoserine lactone, isoleucine methyl ester, leucine methyl ester, norleucine methyl ester, norvaline methyl ester, cyclohexylalanine methyl ester, phenylalanine methyl ester, or glutamic acid dimethyl ester.



3980

Preparation 2

4-Bromo-2-phenylbenzoyl methionine methyl ester

Preparation 2A

4-Bromo-2-phenylbenzoic acid methyl ester

3985 A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous HBr is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

3990

Preparation 2B

4-Bromo-2-phenylbenzoic acid

3995 To a solution of the resultant compound from Preparation 2A (1.0 equivalent) in a 3:1 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Preparation 2C4000 4-Bromo-2-phenylbenzoyl methionine methyl ester

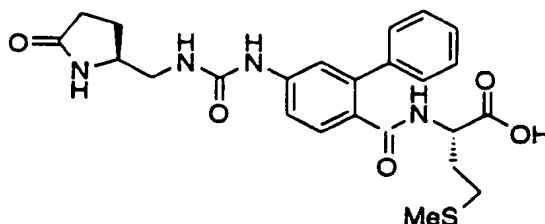
To a solution of the resultant compound from Preparation 2B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Preparation 2D4010 4-Bromo-2-phenylbenzoyl methionine methyl ester alternate procedure

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous HBr is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

Preparation 3Arylbromides of the formula B-Br

The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Preparation 2 to provide the arylbromides listed in Table 2.

Example 14025 4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionineExample 1AMethyl 4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoate

To a solution of methyl 4-amino-2-phenylbenzoate hydrochloride (1.0 equivalent) in
4030 toluene is added triphosgene (0.33 equivalent) and the mixture is heated at reflux until
judged complete by TLC analysis. The intermediate is reacted without further
purification with (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine
(2.0 equivalents). When judged complete by TLC analysis, the reaction is taken up in
ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by
4035 chromatography on silica gel.

Example 1B

4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoic acid

To a solution of the resultant compound from Example 1A (1.0 equivalent) in a 3:1
4040 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of
LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated
and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate
which is dried and evaporated prior to purification by chromatography on silica gel.

Example 1C

4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 1B (1.0 equivalent) in
dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5
4050 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-
dimehtylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When
judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is
washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude
reaction mixture is purified by column chromatography to afford the title product.

Example 1D

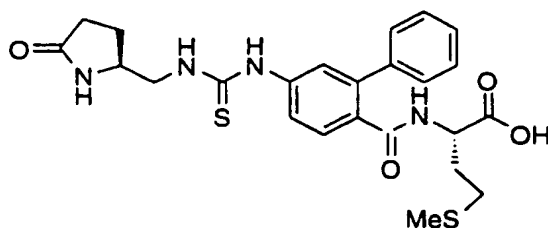
4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in
4060 methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and
triethylamine (2.0 equivalents). The intermediate is reacted without further purification
with (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0
equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl
acetate and washed with 1N HCl and brine, evaporated, and purified by
4065 chromatography on silica gel.

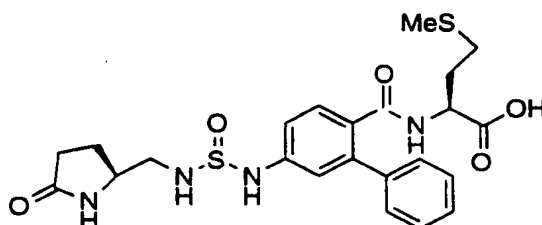
Example 1E

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 1C in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Example 24-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)amino-2-phenylbenzoyl methionine

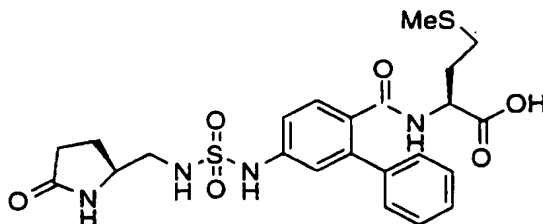
The title compound is prepared as described in Example 1 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

Example 34-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionineExample 3A4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added thionyl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 3B4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 3A in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Example 44-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionineExample 4A4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added sulfonyl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 4B4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate procedure

A solution of 1 equivalent of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and sulfonyl chloride (1.0 equivalent) in acetonitrile with a catalytic amount of antimony(V) chloride is heated to reflux until judged complete by TLC analysis. The solution is then cooled, filtered, and all volatiles are removed under reduced pressure. The residue is taken up in dichloromethane and treated with triethylamine (1 equivalent) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent). When the reaction is judged complete by

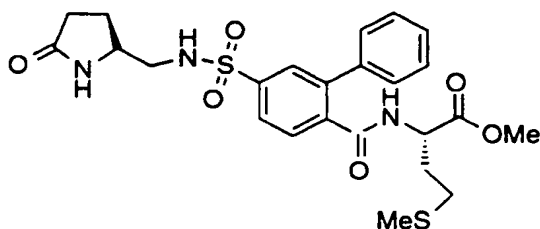
4125 TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 4C

4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

4130

The resultant compound from Example 4A is hydrolyzed according to the procedure of Example 1B to give the title product.



4135

Example 5

4-((S)-2-Pyrrolidone-5-methylaminosulfonyl)-2-phenylbenzoyl methionine

Example 5A

4140

4-Chlorosulfonyl-2-phenylbenzoic acid methyl ester

To a solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists. The chlorodiazonium salt is poured into a solution of sulfur dioxide (10 equivalents), copper (II) chloride (0.5 equivalent) and KCl (1.1 equivalents) in dioxane. When TLC analysis indicated that the reaction is complete, the mixture is diluted with water and extracted into benzene which is dried and evaporated to give the title sulfonyl chloride

4145

Example 5B

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid methyl ester

4150

To a solution of the resultant compound from Example 5A (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

4155

Example 5C

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 5B is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 5D

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 5C (1.0 equivalent) in (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 5E

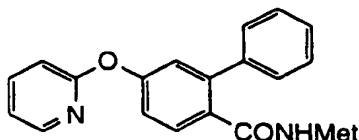
4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists at which time the chlorodiazonium salt will be treated with gaseous sulfur dioxide and copper (II) chloride to give the sulfonyl chloride (0.1 equivalent). This intermediate is reacted with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent) according to the procedure of Example 5B to give the title compound.

Example 5F

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 5D (1.0 equivalent) in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.



Example 64-(2-pyridyloxy)-2-phenylbenzoylmethionineExample 6A4-Hydroxy-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

Example 6B4-(2-Pyridyloxy)-2-phenylbenzoic acid methyl ester

A solution of the resultant phenol from Example 6A (1.0 equivalent) is treated with 2-bromopyridine (1.0 equivalent) in the presence of a NaH (1.0 equivalent), or K₂CO₃ (2.0 equivalents) and copper (1.0 equivalent) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6C4-(2-Pyridyloxy)-2-phenylbenzoic acid

A solution of the resultant ester from Example 6B (1.0 equivalent) in aqueous methanol is treated with NaOH (2.0 equivalents) and stirred until the reaction is deemed complete by TLC analysis. The mixture is acidified, diluted with water, and extracted into ethyl acetate which is dried and evaporated. Chromatography on silica gel provides the title product.

Example 6D4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 6C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 6E4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester, alternate procedure

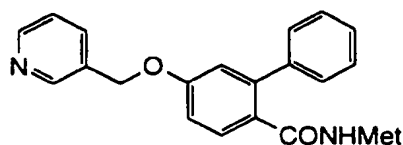
A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated to form the phenol which is purified by chromatography on silica gel. A solution of this phenol (1.0 equivalent) is treated with 3-bromopyridine (1.0 equivalent) in the presence of a

NaH (1.0 equivalent), or K₂CO₃ (2.0 equivalents) and copper (1.0 equivalent) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6F

4-(2-pyridyloxy)-2-phenylbenzoylmethionine

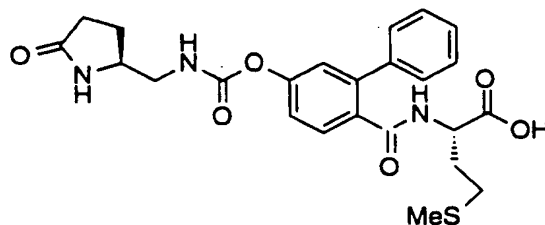
The resultant compound from Example 6E is hydrolyzed according to the procedure of Example 1B to give the title compound.



Example 7

4-(3-pyridylmethylenoxy)-2-phenylbenzoylmethionine

The title compound is prepared as described in Example 6 with the exception that 2-bromopyridine is replaced by 3-chloromethylpyridine hydrochloride.



Example 8

4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

Example 8A

4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine methyl ester

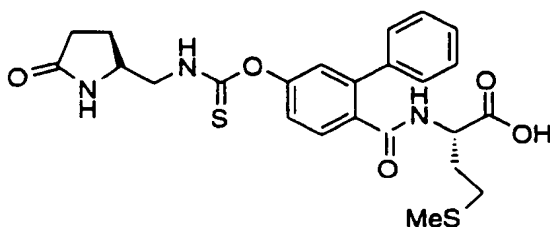
To a solution of 4-hydroxy-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) from Example 6E in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged complete by TLC analysis, the solvent is evaporated with toluene chasers. The chloroformate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone

(1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 8B

4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

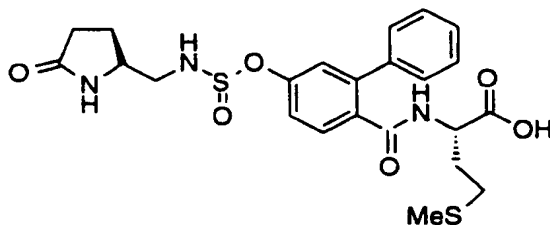
The resultant compound from Example 8A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 9

4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxy-2-phenylbenzoyl methionine methyl ester

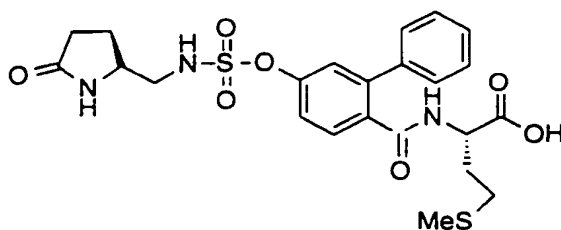
The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by thiophosgene.



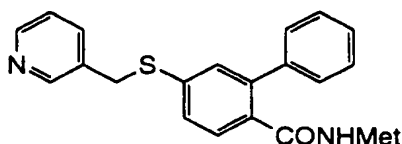
Example 10

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfinyloxy-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride.

**Example 11****4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyloxy)-2-phenylbenzoyl methionine**

The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by sulfuryl chloride.

**Example 12****4-(3-Pyridylmethylthio)-2-phenylbenzoylmethionine****Example 12A****4-Mercapto-2-phenylbenzoic acid methyl ester**

A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with NaNO_2 (1.1 equivalents) to form the diazonium salt. The reaction is treated with S_8 (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel.

Example 12B**4-(2-Pyridylmethylthio)-2-phenylbenzoic acid methyl ester**

A solution of the resultant thiophenol (1.0 equivalent) from Example 12A is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K_2CO_3 (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 12C4-(2-Pyridylthiomethylen)-2-phenylbenzoic acid

The resultant compound from Example 12B is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 12D4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 12C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 12E4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 1

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with NaNO_2 (1.1 equivalents) to form the diazonium salt. The reaction is treated with S_8 (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. The thiophenol is purified by chromatography on silica gel. A solution of this thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K_2CO_3 (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 12F4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 2

Methyl 4-amino-2-phenylbenzoate (100 mmol) is mixed in 50% sulfuric acid, and is cooled by a ice-water bath. To the above mixture with good stirring is added slowly a cold solution of sodium nitrite (110 mmol) in water, the reaction temperature is kept under 10°C .

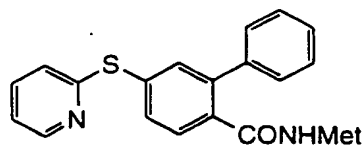
Powdered anhydrous sodium carbonate (100 mmol) is carefully added to the cold reaction mixture in small portions, until the reaction mixture reaches pH 7 to 8. Then, the reaction mixture is added in small portions to a solution of sodium p-methoxybenzylsulfide (prepared from reaction 110 mmol of p-methoxybenzylthiol with 55 mmol of 2.0 M NaOH aqueous solution). After completion of the addition, the reaction mixture is refluxed until judged complete by TLC analysis. The reaction mixture is then extracted with ether, and the organic extracts are washed sequentially with aqueous sodium carbonate solution, water and

brine, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The product thus obtained is dissolved in methanol and water, followed by addition of lithium hydroxide (200 mmol),
4355 and the mixture is refluxed until hydrolysis is judged complete by TLC analysis. The reaction mixture is then acidified with 6 N HCl, and extracted into ethyl acetate. The organic extracts are washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The crude product obtained is redissolved in methylene chloride, followed by addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.1 equivalent)
4360 and 1-hydroxybenzotriazole (1.2 equivalent). The reaction is stirred until it is judged complete by TLC analysis, and then is diluted with ether. The mixture is washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The resulting product is dissolved in trifluoroacetic acid and anisole (1.5 equivalent), and mercury diacetate (1.2
4365 equivalent) is added. After TLC shows no starting material left, the reaction mixture is diluted with ether, washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude material is purified by column chromatography to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. A solution of this thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0
4370 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 12G

4-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

The resultant compound from Example 12D is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 134-(2-Pyridylthio)-2-phenylbenzoylmethionineExample 13A4-Fluoro-2-phenyl benzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous HBF_4 is treated with NaNO_2 (1.1 equivalents) until an excess of nitrous acid persists. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

Example 13B4-Fluoro-2-phenyl benzoic acid

The resultant compound from Example 13A is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 13C4-Fluoro-2-phenyl benzoyl methionine methyl ester

The resultant product from Example 13B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 13D4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester

A mixture of the resultant fluorobenzoate from Example 13C (1.0 equivalent) and 2-mercaptopyridine (1.0 equivalent) is treated with K_2CO_3 (2.0 equivalents) or NaH (1.0 equivalent) in DMF or DMSO and is stirred until the reaction is judged complete by TLC analysis. The mixture is diluted with water and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 13E4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 1

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with NaNO_2 (1.1 equivalents) to form the diazonium salt. The

4415 reaction is treated with S₈ (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel. A solution of this thiophenol (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalent), or K₂CO₃ (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

4420

Example 13F

4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 2

4425 A solution of the resultant thiophenol from Example 12A (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel. The resultant ester is hydrolyzed according to the procedure of Example 6C and then is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

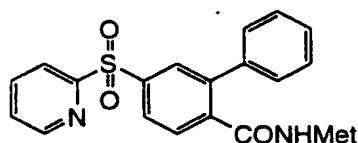
4430

Example 13G

4-(2-Pyridylthio)-2-phenylbenzoylmethionine

The resultant compound from Example 13D is hydrolyzed according to the procedure of Example 1B to give the title product.

4435



Example 14

4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

4440

Example 14A

4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid methyl ester

4445 A solution of 4-(2-pyridylthio)-2-phenylbenzoic acid methyl ester (Example 13F) is carefully treated with two equivalents of *meta*-chloroperbenzoic acid in methylene chloride at low temperature and the reaction is then quenched with aqueous Na₂SO₃ when judged complete by TLC analysis. The layers are separated and the organic phase is extracted with

aqueous NaHCO_3 to remove the *m*-chlorobenzoic acid. The product is isolated by removal of the solvent and is purified by chromatography on silica gel.

4450

Example 14B4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 14A is hydrolyzed according to the procedure of Example 6C to give the title acid.

4455

Example 14C4-(2-pyridylsulfonyl)-2-phenylbenzoylmethionine methyl ester

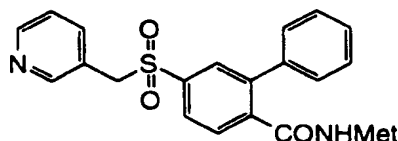
The resultant product from Example 14B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

4460

Example 14D4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

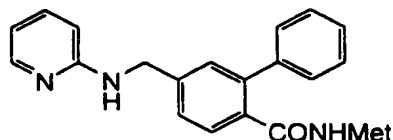
The resultant compound from Example 14C is hydrolyzed according to the procedure of Example 1B to give the title product.

4465

Example 154-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

4470

The title compound is prepared from the resultant product of Example 12B using the procedures from Example 14.



4475

Example 164-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

Example 16A4480 2-Phenylterephthalic acid mono methyl ester

A solution of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), Pd(OAc)₂ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

Example 16B4-(Hydroxymethyl)-2-phenylbenzoic acid methyl ester

The resultant acid from Example 16A (1.0 equivalent) is treated with a slight excess of N-methylmorpholine (1.1 equivalent) and isobutylchloroformate (1.0 equivalent) in THF at 0° C. The mixture is then treated with NaBH₄ (1.0 equivalent) and aqueous NaHCO₃ and stirred at 0° C until the reaction is judged complete by TLC analysis. The mixture is poured into dilute aqueous acid and extracted into ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

Example 16C4-(Hydroxymethyl)-2-phenylbenzoic acid

The resultant compound from Example 16B is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 16D4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester

The resultant product from Example 16C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 16E4-formyl-2-phenylbenzoyl methionine methyl ester

A mixture of the resultant alcohol from Example 16D (1.0 equivalent), N-methylmorpholine-N-oxide (1.5 equivalents), molecular sieves, and a catalytic amount of TPAP is stirred in a CH₂Cl₂/acetonitrile mixture until the reaction is judged complete by TLC analysis. The mixture is diluted with ethyl ether and filtered through SiO₂. The product is purified by chromatography on silica gel.

Example 16F4-(formyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

A mixture of (2-phenyl-4-bromobenzoyl) methionine methyl ester (100 mmol), 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (100 mmol), tetrakis(triphenylphosphine)palladium (0) (3 mmol) in toluene and 2 M sodium carbonate in water (100 mL) is heated at 80 °C until the starting methyl ester disappears. The resulting mixture is extracted with ether, and washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. To a solution of the resulting vinyl compound in dioxane/water (4/1) is added osmium tetraoxide (0.03 equivalent), N-methylmorpholine N-oxide (3 equivalents), and the reaction is stirred at 25 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

Example 16G4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

To a solution of the resultant compound from Example 16E in ethanol at 0 °C is added sodium borohydride (0.5 equivalent), and the reaction is stirred at 0 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

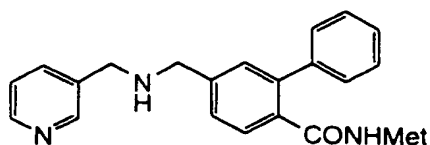
Example 16H4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant aldehyde from Example 16E (1.0 equivalent), 2-aminopyridine (1.0 equivalent) and NaCNBH₃ (1.5 equivalents) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO₃ and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 16I4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

The resultant compound from Example 16H is hydrolyzed according to the procedure of Example 1B to give the title product.

4555

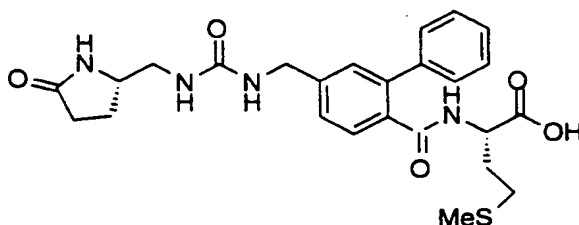


Example 17

4560

4-[(3-aminomethylpyridyl)methylene]-2-phenylbenzoyl methionine

Using the procedures of Examples 16F-G and replacing 2-aminopyridine with 3-aminomethylpyridine affords the title product.



4565

Example 18

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

4570

Example 18A

4-(Azidomethyl)-2-phenylbenzoyl methionine methyl ester

To triphenylphosphine (1.0 equivalent) in tetrahydrofuran (THF) at -78°C is added diethyl azodicarboxylate (1.0 equivalent) in THF. To this mixture is added a solution of hydrazoic acid in benzene (2.0 equivalents) and then the resultant compound from Example 16D (1.0 equivalent). After one hour the mixture was warmed to room temperature, stirred until the reaction is judged complete by TLC analysis, evaporated and chromatographed on silica gel to afford the title product.

4575

Example 18B

4580

4-(Aminomethyl)-2-phenylbenzoyl methionine methyl ester

To the resultant compound from Example 18A in methanol is added triethylamine (3.0 equivalent) and propane 1,3-dithiol (3.0 equivalents). After the reaction is judged complete

by TLC analysis, the mixture is filtered and evaporated. Chromatography of the residue on silica gel provides the title product.

Example 18C

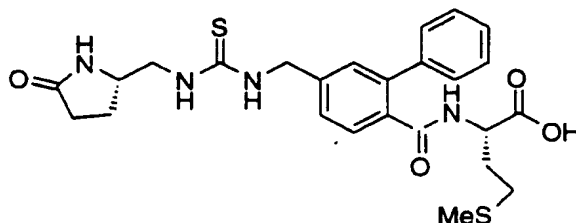
4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 18B (1.0 equivalent) in methylene chloride is added triphosgene (0.33 equivalent) and triethyl amine (2.0 equivalents). This intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 18D

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

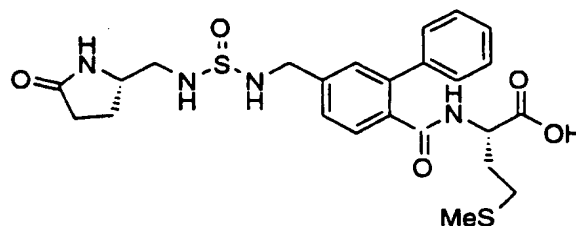
The resultant compound from Example 18C is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 19

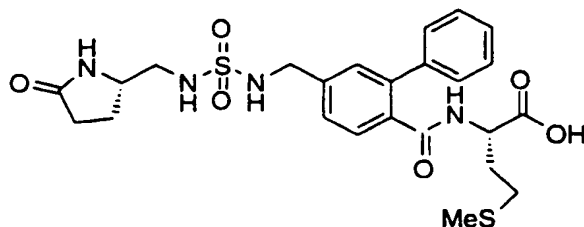
4-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

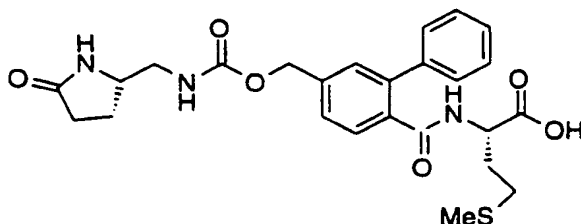


Example 204-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)aminomethyl-2-phenylbenzoyl methionine

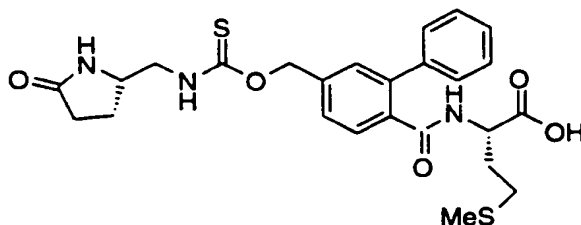
The title compound is prepared as described in Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent).

Example 214-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)aminomethyl-2-phenylbenzoyl methionine

Using the Procedure of Example 4 with the resultant compound from Example 18B affords the title product.

Example 224-((S)-2-Pyrrolidone-5-aminomethyl(carbonyloxymethylene)-2-phenylbenzoyl methionine

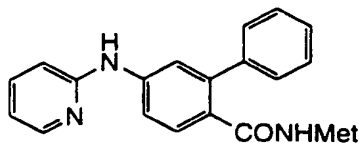
Using the procedure of Example 8 with the resultant compound from Example 16D provides the title product.

Example 23

4635 4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxymethylene)-2-phenylbenzoyl
methionine

Using the procedure of Example 8 with the resultant compound from Example 16D and replacing triphosgene (0.33 equivalent) with thiophosgene (1.0 equivalent) provides the title product.

4640



Example 24

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

4645

Example 24A

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine methyl ester

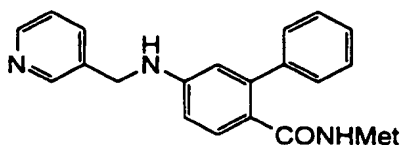
4-Amino-2-phenylbenzoyl methionine (1.0 equivalent) methyl ester and 2-bromopyridine hydrobromide (1.0 equivalent) in pyridine are heated until the reaction is judged complete by
4650 TLC analysis. The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 24B

4655

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

The resultant compound from Example 24A is hydrolyzed according to the procedure of Example 1B to give the title product.



4660

Example 25

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

Example 25A

4665

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine methyl ester

A mixture of 3-pyridinecarboxaldehyde (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and NaCNBH₃ (1.0 equivalent) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO₃ and extracted into ethyl acetate which is dried and evaporated.

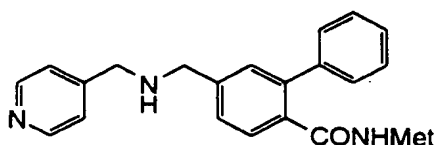
4670 Chromatography of the residue on silica gel affords the title compound.

Example 25B

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

The resultant compound from Example 25A is hydrolyzed according to the procedure of Example 1B to give the title product.

4675



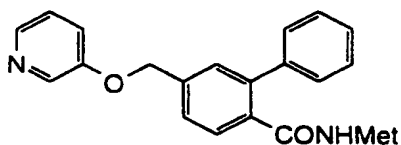
4680

Example 26

4-[(4-aminomethylpyridyl)methylene]-2-phenylbenzoylmethionine

Using the procedures of Examples 25 with the resultant amine from Example 18B and 3-pyridinecarboxaldehyde affords the title product.

4685



Example 27

4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

4690

Example 27A

4-(p-Toluenesulfonyloxy)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 16D (1.0 equivalent) and *p*-toluenesulfonyl chloride (1.0 equivalent) in pyridine are stirred until the reaction is judged complete by TLC analysis.

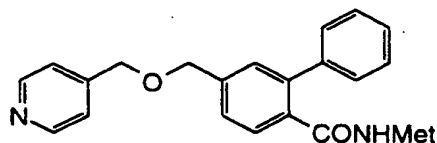
4695 The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 27B4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine methyl ester

3-Hydroxypyridine (1.0 equivalent) is treated with sodium hydride (1.0 equivalent) in DMSO, then the resultant compound from Example 27A (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

Example 27C4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

The resultant compound from Example 27B is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 284-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionineExample 28A4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

Using the procedure of Example 27B but replacing 3-hydroxypyridine with 3-hydroxymethylpyridine affords the title compound.

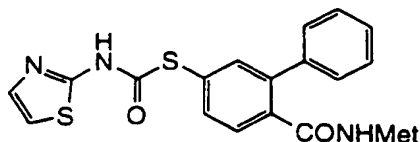
Example 28B4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester, alternate procedure

The resultant compound from Example 16D (1.0 equivalent) is treated with sodium hydride (2.0 equivalents) in DMSO, then 3-chloromethylpyridine hydrochloride (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

Example 28C

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 28A is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 29{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionineExample 29AThiazol-2-ylisocyanate

A solution of 2-aminothiazol (1.0 mmol), triphosgene (0.34 mmol) and triethylamine (1.0 mmol) in toluene (10 mL) is refluxed until TLC shows no starting amine left. The solvent is then removed in vacuo, and the resulting material is used without further purification.

Example 29B{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester

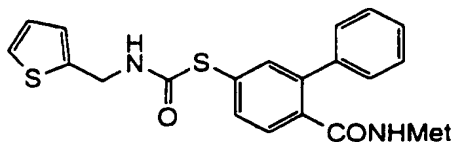
A solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1.0 mmol) and the isocyanate prepared in example 29A (1.0 mmol) in THF is refluxed until TLC shows no thiol left. The solvent is then evaporated in vacuo, and the residue is purified by column chromatography on silica gel to give the title compound.

Example 29C{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester, alternate procedure

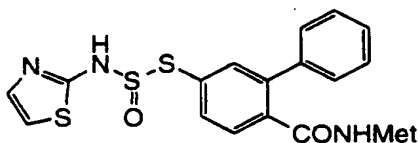
To a solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1 equivalent) in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged complete by TLC analysis, the solvent is evaporated with toluene chasers. The thiochloroformate is reacted without further purification with 2-aminothiazol (1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 29D{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine

The resultant compound from Example 29B is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 30{2-Phenyl-4-[(thien-2-ylmethylamino)carbonylthio]benzoyl}-methionine

Using the procedure of Example 29 but replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

Example 31{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionineExample 31A(N-Thionyl)thiazol-2-ylamine

A solution of 2-aminothiazol (1.0 mmol), in thionyl chloride is heated at reflux until the reaction is judged to be complete by TLC analysis. Then, the excess thionylchloride is distilled out in vacuo. The resulting material is used without further purification.

Example 31B{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester

Using the procedure of Example 29B but replacing the resultant product from Example 29A with the resultant product from Example 31A affords the title compound.

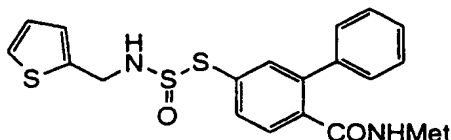
Example 31C{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester, alternate procedure

Using the procedure of Example 29C but replacing phosgene in toluene with thionyl chloride affords the title compound.

Example 31D

{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine

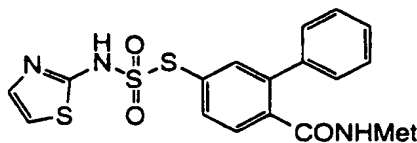
The resultant compound from Example 31B is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 32

{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthio]benzoyl}-methionine

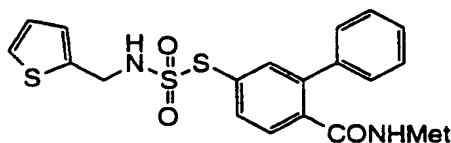
Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 33

{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthio]benzoyl}-methionine methyl ester

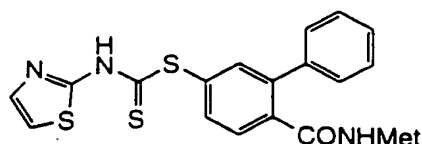
Using the procedure of Example 31 but replacing thionyl chloride with sulfonyl chloride affords the title product.



Example 34

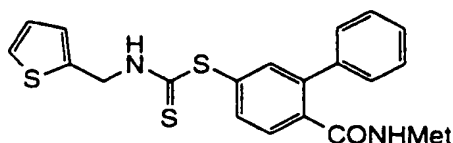
{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthio]benzoyl}-methionine

Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-ylmethylamine and replacing thionyl chloride with sulfonyl chloride affords the title product.

Example 35

4830 [2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthio]benzoyl]-methionine

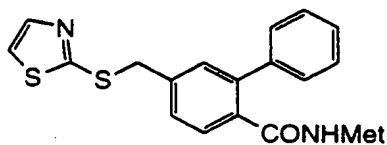
Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.

Example 36

4835 [2-Phenyl-4-[(thien-2-ylmethylamino)thiocarbonylthio]benzoyl]-methionine

Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4840

Example 37

[2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl]-methionine

4845

Example 37A

[2-Phenyl-4-[thiomethyl]benzoyl]-methionine methyl ester

The resultant product from Example 27A is dissolved DMF/water (2/1), and sodium hydrosulfide (5 equivalent) is added to the reaction mixture. The reaction is stirred until

4850 TLC analysis shows that the reaction is complete. Then, the reaction mixture is acidified with 3 N HCl to about pH 4, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified with column chromatography on silica gel to give the title compound.

4855

Example 37B

[2-Phenyl-4-[thiomethyl]benzoyl]-methionine methyl ester, alternate procedure

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16D (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

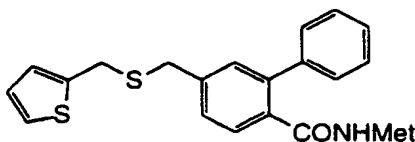
Example 37C

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine methyl ester

A mixture of the resultant thiol from Example 37A (1 mmol), 2-bromothiazole (1.5 mmol), and anhydrous potassium carbonate (5 mmol) in DMF is stirred at 100 °C until TLC analysis shows that the starting thiol disappeared. Then, the reaction mixture is diluted with water, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified by column chromatography on silica gel to give the title compound.

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine

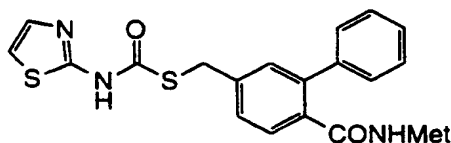
The resultant compound from Example 37C is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 38

{2-Phenyl-4-[(thien-2-yl)methyl]thiomethyl]benzoyl}-methionine

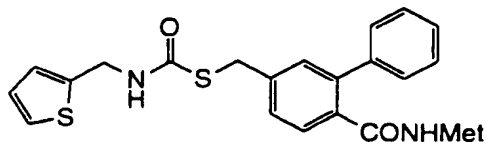
Using the procedure of Example 37 and replacing 2-bromothiazole with 2-bromomethylthiophene affords the title product.



Example 39

{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

4890 Using the procedure of Example 29 with the resultant product from Example 37A affords the title product.

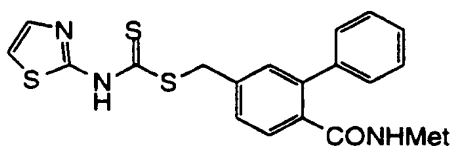


4895

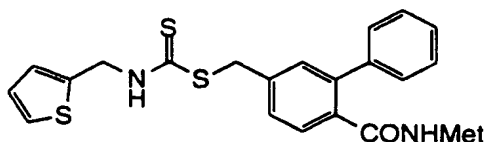
Example 40{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4900

Example 41{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

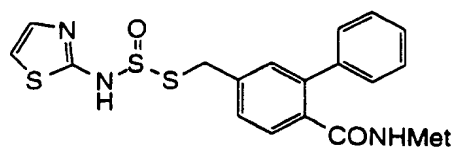
4905 Using the procedure of Example 29 with the resultant product from Example 37A and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.



4910

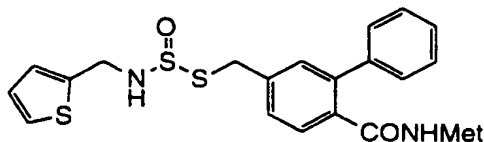
Example 42{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

4915 Using the procedure of Example 29 with the resultant product from Example 37A, replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol), and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

**Example 43**

4920 {2-Phenyl-4-[(thiazol-2-ylamino)thionylthiomethyl]benzoyl}-methionine

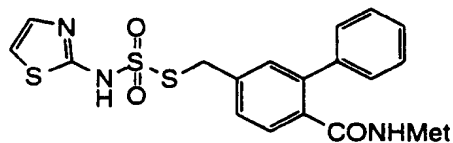
Using the procedure of Example 31 with the resultant product from Example 37A affords the title product.

**Example 44**

4925 {2-Phenyl-4-[(thien-2-ylmethylamino)thionylthiomethyl]benzoyl}-methionine

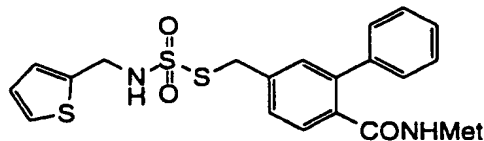
Using the procedure of Example 31 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4930

**Example 45**

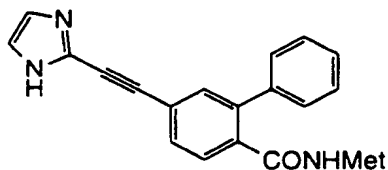
4935 {2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 31 with the resultant product from Example 37A and replacing thionyl chloride with sulfonyl chloride affords the title product. affords the title product.

**Example 46**

4940 {2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 31 with the resultant product from Example 37A, replacing thionyl chloride with sulfuryl chloride, and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 47

(4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl)methionine

Example 47A

(4-Ethynyl-2-phenylbenzoyl)methionine methyl ester

A mixture of (2-phenyl-4-bromobenzoyl)-methionine methyl ester (100 mmol), diethylamine (300 mmol), trimethylsilylacetylene (110 mmol), bis(triphenylphosphine) palladium diacetate (5 mmol) and copper(I) iodide (3 mmol) in toluene is heated at 60 °C until TLC analysis indicates the starting methyl ester has disappeared. The reaction mixture is concentrated in vacuo, redissolved in ether, filtered through silica gel, and concentrated. The residue is then dissolved in THF, and is treated with tetrabutylammonium fluoride (120 mmol). After TLC analysis indicates that no starting material is left, the reaction mixture is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified with column chromatography on silica gel to give the title product.

Example 47B

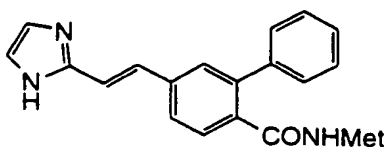
(4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl)-methionine methyl ester

The resultant product from Example 47A (5 mmol) is mixed with 4-bromoimidazole (5 mmol), diethylamine (1 mL), bis(triphenylphosphine) palladium diacetate (0.1 mmol) and copper(I) iodide (0.1 mmol) in toluene. The mixture is stirred at 25 °C until TLC analysis indicates the reaction is complete. The reaction mixture is concentrated in vacuo, and the residue is purified with column chromatography on silica gel to give the title product.

Example 47C

(4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl)-methionine

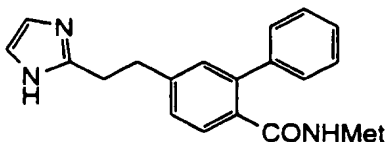
The resultant compound from Example 47B is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 48

{4-[2-(Imidazol-4-yl)ethenyl]-2-phenylbenzoyl}-methionine

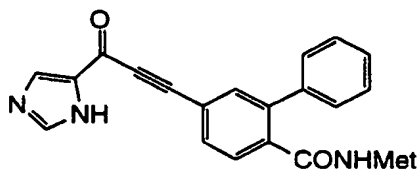
The resultant acetylene (3 mmol) from Example 47 is mixed with Lindlar catalyst (50 mg), 5 drops of quinoline in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.



Example 49

{4-[2-(Imidazol-4-yl)ethyl]-2-phenylbenzoyl}-methionine

The resultant olefin (1 mmol) from Example 48 is mixed with 5% palladium on carbon (100 mg) in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.



Example 50

{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine

Example 50A

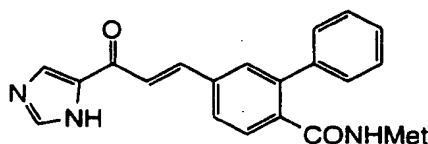
{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine methyl ester

5005 A stainless autoclave containing the resultant product from Example 47A (5 mmol), 4-bromoimidazole (5 mmol), 1,1'-bis(diphenylphosphine)-ferrocenepalladium dichloride (0.1 mmol), and triethylamine (10 mL) is flushed with nitrogen, and pressurized to 20 atm with carbon monoxide. The reaction mixture is stirred at 120 °C until judged complete by TLC analysis. After cooling, the triethylamine is evaporated in vacuo, and the residue is purified
5010 by column chromatography on silica gel to give the title compound.

Example 50B

{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine

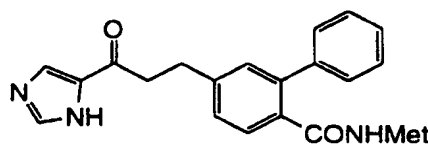
5015 The resultant compound from Example 50A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 51

5020 {4-[2-(Imidazol-4-ylcarbonyl)ethenyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 48 with the resultant compound from Example 50 affords the title product.



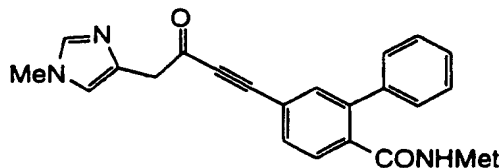
5025

Example 52

{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 49 with the resultant compound from Example 51 affords the title product.

5030



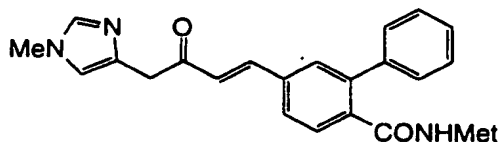
Example 53

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyryl]-2-phenylbenzoyl}-methionineExample 53A{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyryl]-2-phenylbenzoyl}-methionine methyl ester

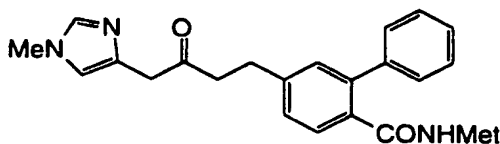
To a solution of 1-methyl-4-imidazoleacetic acid (5 mmol) in methylene chloride at 0 °C is added oxalyl chloride (6 mmol) and DMF (0.05 mmol). After 30 minute, the solvent is evaporated in vacuo. The residue is redissolved in dichloromethane, followed by the addition of the resultant acetylene from Example 47A (5 mmol), triethylamine (10 mmol), and copper(I) iodide (1 mmol). The reaction is stirred at 25 °C until TLC analysis indicates no starting material is left in the reaction mixture. The reaction is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to give the title compound.

Example 53B{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyryl]-2-phenylbenzoyl}-methionine

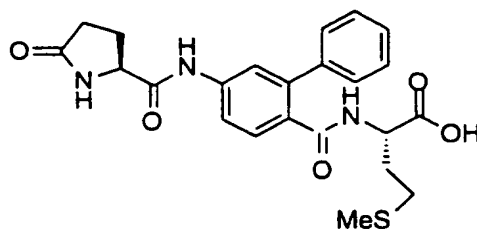
The resultant compound from Example 53A is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 54{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyryl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 48 with the resultant compound from Example 53 affords the title product.

Example 55{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyryl]-2-phenylbenzoyl}-methionine

5065 Using the procedure of Example 49 with the resultant compound from Example 53 affords the title product.



5070 Example 56

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

Example 56A

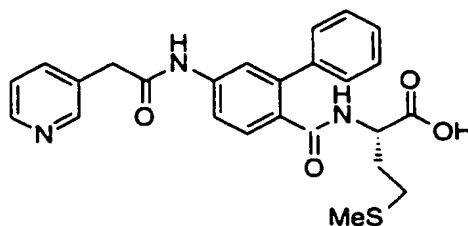
(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine methyl ester

5075 To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N
5080 HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 56B

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

5085 The resultant compound from Example 56A is hydrolyzed according to the procedure of Example 1B to give the title product.

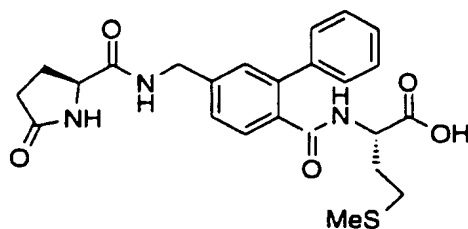


5090 Example 57

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

Using the procedure of Example 56 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.

5095

Example 58

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

5100

Example 58A

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine methyl ester

To a solution of the resultant amine from Example 18B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

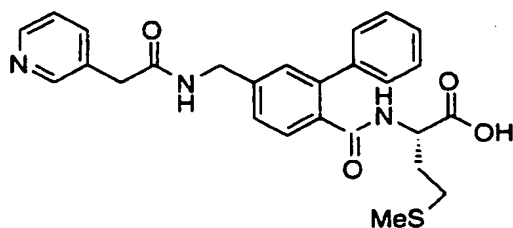
5110

Example 58B

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

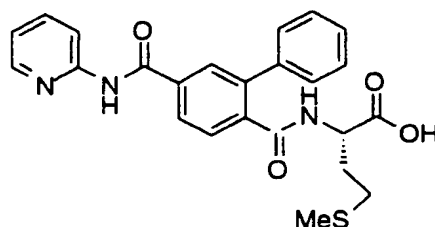
The resultant compound from Example 58A is hydrolyzed according to the procedure of Example 1B to give the title product.

5115

Example 59

naming error((S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine)

Using the procedure of Example 58 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.



Example 60

4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

Example 60A

4-Carboxy-2-phenylbenzoyl methionine methyl ester

A solution of 4-bromo-2-phenylbenzoyl methionine methyl ester (1.0 equivalent), Pd(OAc)₂ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

Example 60B

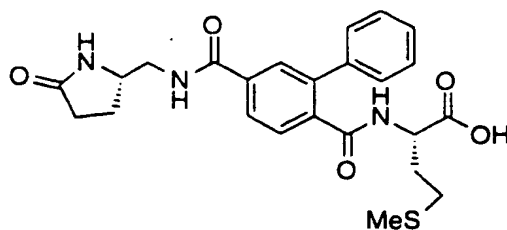
4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant acid from Example 60A (1.0 equivalent) in DMF is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

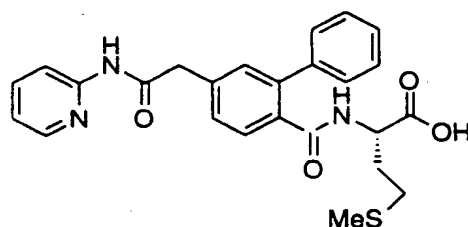
Example 60C

4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

The resultant compound from Example 60B is hydrolyzed according to the procedure of Example 1B to give the title product.

**Example 61****4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyl-2-phenylbenzoyl methionine**

Using the procedure of Example 60 and replacing 2-aminopyridine with (S)-5-aminomethyl-2-pyrrolidone affords the title product.

**Example 62****4-[(pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine****Example 62A****4-Diazocarbonyl-2-phenylbenzoyl methionine methyl ester**

The resultant acid from Example 60A (1 equivalent) in dichloromethane is treated with oxalyl chloride (1 equivalent) and DMF (0.05 equivalent). When gas evolution has ceased, the acid chloride solution is added to an ether solution of diazomethane. The reaction is stirred until judged complete by TLC analysis, and then is concentrated to give the crude title compound which is purified by chromatography on silica gel.

Example 62B**4-carboxymethyl-2-phenylbenzoyl methionine methyl ester**

The resultant compound from Example 62A (1 equivalent) in dioxane is added to a slurry of sodium thiosulfate (1.1 equivalents) and silver (I) oxide (0.5 equivalent) in water. The reaction is stirred until judged complete by TLC analysis, filtered, acidified, and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title product.

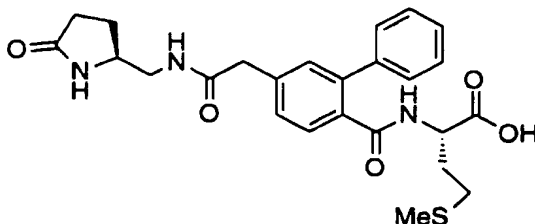
Example 62C

4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine methyl ester

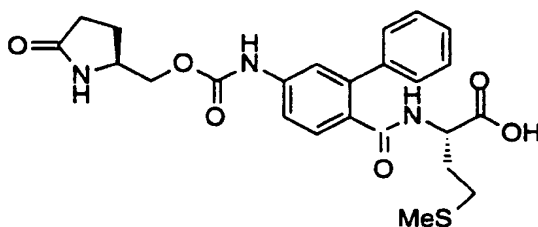
To a solution of the resultant acid from Example 62B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 62D4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

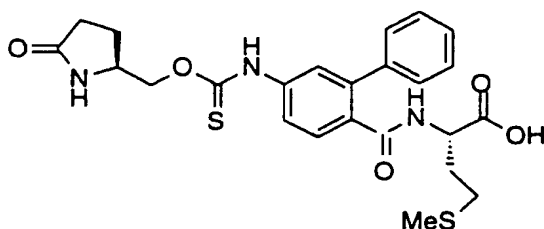
The resultant compound from Example 62C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 634-[(S)-2-Pyrrolidone-5-aminomethyl]carbonylmethyl-2-phenylbenzoyl methionine

Using the procedure of Example 62 and replacing 2-aminopyridine with (S)-5-aminomethyl-2-pyrrolidone affords the title product.

Example 644-[(S)-2-Pyrrolidone-5-methoxycarbonyl]amino-2-phenylbenzoyl methionine

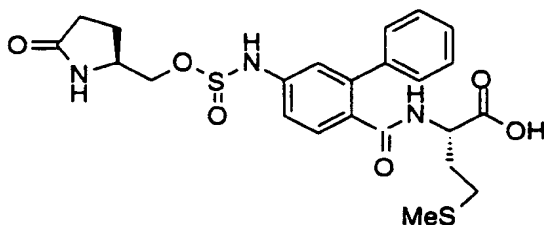
The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

**Example 65**

5210 4-((S)-2-Pyrrolidone-5-methoxythiocarbonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

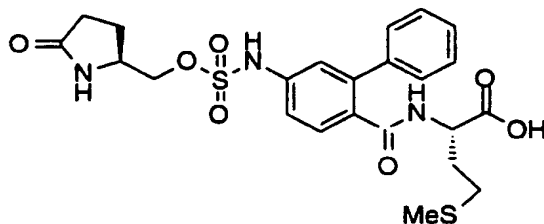
5215

**Example 66**

5220 4-((S)-2-Pyrrolidone-5-methoxysulfinyl)amino-2-phenylbenzoyl methionine

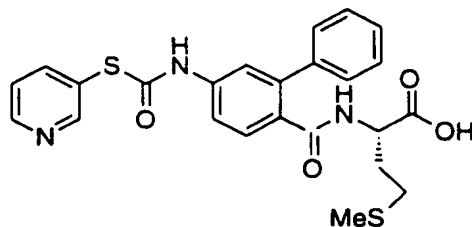
The title compound is prepared as described in Example 3 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

5225

**Example 67**

4-((S)-2-Pyrrolidone-5-methoxysulfonyl)amino-2-phenylbenzoyl methionine

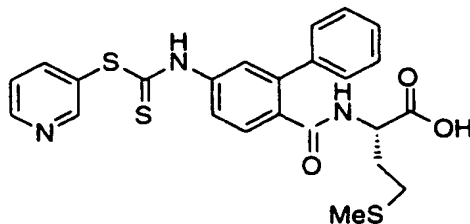
The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 68

4-(Pyridin-3-ylmercaptocarbonyl)amino-2-phenylbenzoyl methionine

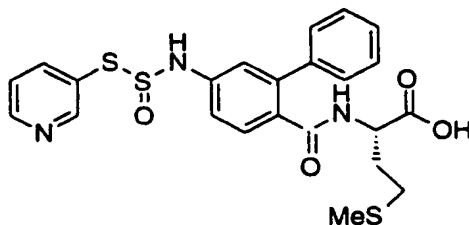
The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 69

4-(Pyridin-3-ylmercaptothiocabonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

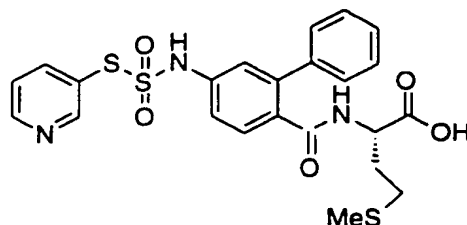


Example 70

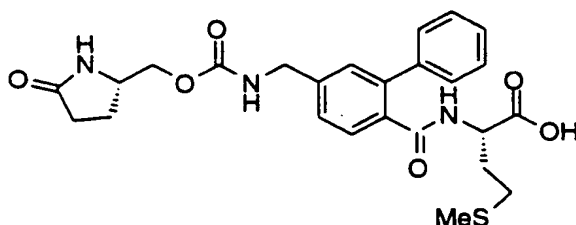
4-(Pyridin-3-ylmercaptosulfinyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5255

Example 714-(Pyridin-3-ylmercaptosulfonyl)amino-2-phenylbenzoyl methionine

5260 The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

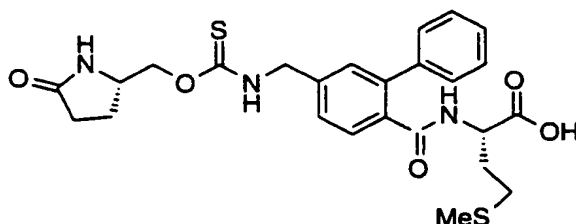


5265

Example 724-((*S*)-2-Pyrrolidone-5-methoxycarbonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

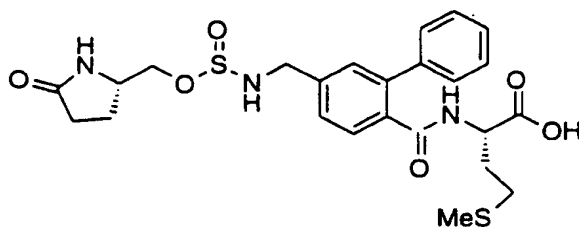
5270

Example 734-((*S*)-2-Pyrrolidone-5-methoxythiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

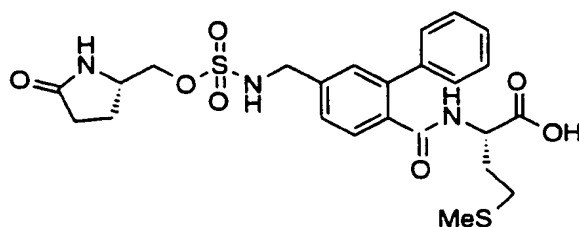
5275

The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

5280

Example 744-((*S*)-2-Pyrrolidone-5-methoxysulfinyl)aminomethyl-2-phenylbenzoyl methionine

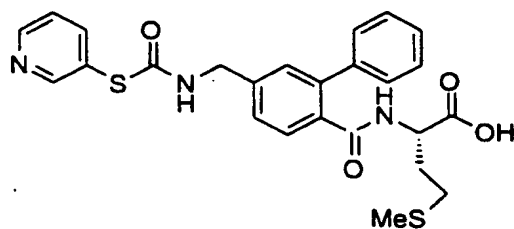
5285 The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



5290

Example 754-((*S*)-2-Pyrrolidone-5-methoxysulfonyl)aminomethyl-2-phenylbenzoyl methionine

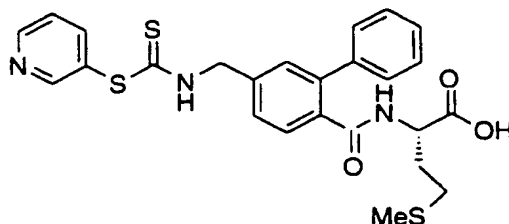
5295 The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

Example 76

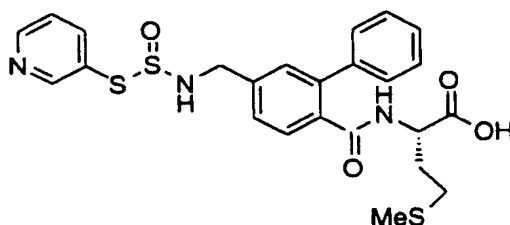
5300 4-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5305

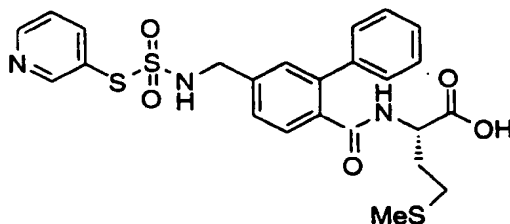
Example 774-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

5310 The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

Example 784-(Pyridin-3-ylmercaptosulfinyl)aminomethyl-2-phenylbenzoyl methionine

5315 The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5320

Example 79

4-(Pyridin-3-ylmercaptosulfonyl)aminomethyl-2-phenylbenzoyl methionine

5325 The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

Example 80A-NH-CO-NH-B

5330 The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products
5335 derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
5340 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 81A-NH-CS-NH-B

5345 The procedure of Example 1 is used with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206
5350 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
5355 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 82A-NH-SO-NH-B

5360 The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-

aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 83

A-NH-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 84

A-NH-SO₂-B

The procedure of Example 5 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 85

A-NH-CO-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 86

A-NH-CS-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thiophosgene and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 87

A-NH-SO-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5435

Example 88A-NH-SO₂-O-B

5440 The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by sulfuryl chloride and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5445 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5450

Example 89A-NH-CH₂-B

5455 The procedure of Example 16 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5460 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 90A-NH-CO-NH-CH₂-B

5465

5470 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 91

A-NH-CS-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 92

A-NH-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 93

A-NH-SO₂-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by sulfuryl chloride (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 94

A-NH-CO-O-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 95

A-NH-CS-O-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thiophosgene and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

5545 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 96

A-NH-CO-S-B

5550 The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from
5555 amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5560

Example 97

A-NH-CS-S-B

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of
5565 Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5570 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5575

Example 98

A-NH-SO-S-B

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of
5580 Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from

amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 99

A-NH-SO₂-S-B

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by sulfuryl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 100

A-NH-CO-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 101A-NH-CS-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 102A-NH-SO-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 103A-NH-SO₂-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by sulfuryl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products

derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 104

A-CO-NH-B

The procedure of Example 56 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and pyroglutamic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 105

A-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 58 with the exception that pyroglutamic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 106

A-CO-C \equiv C-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 53 with the exception that 1-methyl-4-imidazoleacetic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 107

A-CO-CH=CH-B

The products from Example 106 are reacted according to the procedure of Example 54. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 108

A-CO-CH₂-CH₂-B

The products from Example 107 are reacted according to the procedure of Example 55. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

5730 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 109

A-NH-CO-B

5735 The procedure of Example 60 is used with the exception that 4-bromo-2-phenylbenzoyl methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5740 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5745

Example 110

A-NH-CO-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 60A. The resultant carbocyclic acids are reacted according to the procedure of Example 62 with
5750 the exception that 2-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5755 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5760

Example 111

A-CH₂-NH-B

The procedure of Example 25 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an amine from Table 1 (B-NH₂) and 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products
5765 derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is

followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

5770 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

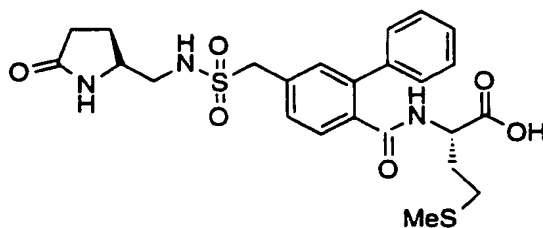
5775

Example 112
A-CH₂-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 25 with the exception that 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

5785 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5795



Example 113
4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethyl)-2-phenylbenzoyl methionine

Example 113A4-Thioacetoxymethyl-2-phenylbenzoic acid methyl ester

5800 To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thioacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16B (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in
5805 methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

Example 113B4-Chlorosulfonylmethylene-2-phenylbenzoic acid methyl ester

5810 The resultant compound from Example 113A in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

5815

Example 113C4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid methyl ester

To a solution of the resultant compound from Example 113B (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0
5820 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 113D4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid

5825 The resultant compound from Example 113C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 113E4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine methyl ester

5830

To a solution of the resultant compound from Example 113D (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimehtylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged

5835 complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 113F

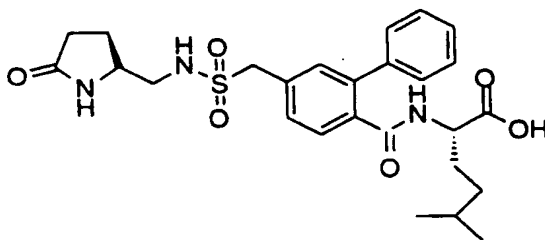
5840 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine

The resultant compound from Example 113E is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 114

A-NH-SO₂-CH₂-B

The procedure of Example 113 is used with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.



Example 115

5855 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethyl-2-phenylbenzoyl leucine

Example 115A

4-(Hydroxymethyl)-2-phenylbenzoyl leucine methyl ester

(2-phenyl-4-bromobenzoyl)-leucine methyl ester is reacted according to the procedures of

5860 Example 16F-G.

Example 115B

4-Thioacetoxymethyl-2-phenylbenzoyl leucine methyl ester

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 115A (1. equivalent) in THF. The

reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

Example 115C

4-Chlorosulfonylmethylene-2-phenylbenzoyl leucine methyl ester

The resultant compound from Example 115B in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

Example 115D

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine methyl ester

To a solution of the resultant compound from Example 115C (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 115E

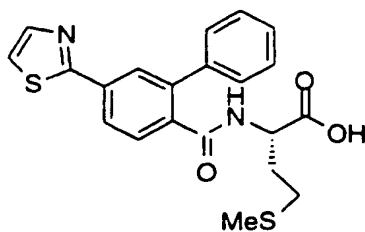
4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine

The resultant compound from Example 115D is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 116

A-NH-SO₂-CH₂-B

The procedure of Example 115 is used with the exception that (2-phenyl-4-bromobenzoyl)-leucine methyl ester is replaced by a bromide from Table 2, entries 28-132 (B-Br) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

Example 1174-(2-Thiazolyl)-2-phenylbenzoyl methionineExample 117A2-Thiazole boronic acid

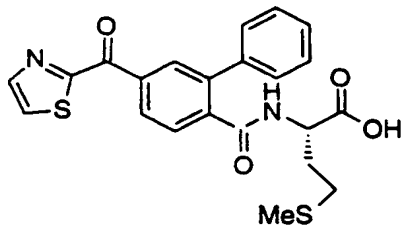
A solution of thiazole (1.0 equivalent) is lithiated with a slight excess of n-butyl lithium in THF (1.05 equivalents) and then treated with trimethyl borate (1.05 equivalents). The reaction mixture is quenched by the addition of aqueous HCl and the resulting boronate ester is cleaved by the addition of excess aqueous NaOH. After acidification and extraction into ethyl acetate the crude boronic acid is used without further purification.

Example 117B4-(2-Thiazolyl)-2-phenylbenzoyl methionine methyl ester

A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole boronic acid (1.0 equivalent) and catalytic $\text{Pd}(\text{PPh}_3)_4$ is heated in a two phase system of toluene and aqueous Na_2CO_3 . After cooling, the resulting biaryl compound is isolated by evaporation of the organic phase and is purified by chromatography on silica gel.

Example 117C4-(2-Thiazolyl)-2-phenylbenzoyl methionine

The resultant compound from Example 117C is hydrolyzed according to the procedure of Example 1B to give the title product.

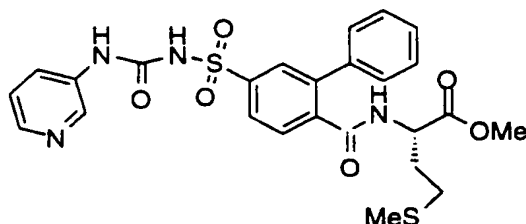
Example 1184-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

Example 118A4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine methyl ester

A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole
boronic acid from Example 117A (1.0 equivalent) and catalytic $\text{Pd}(\text{PPh}_3)_4$ is heated in a two
phase system of toluene and aqueous Na_2CO_3 previously purged with a large excess of
carbon monoxide. The resulting diaryl ketone is isolated by evaporation of the organic
phase and is purified by chromatography on silica gel.

Example 118B4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

The resultant compound from Example 118A is hydrolyzed according to the procedure of
Example 1B to give the title product.

Example 1194-[(3-Aminopyridyl)carbonylamidosulfonyl]-2-phenylbenzoylmethionineExample 119A4-Aminosulfonyl-2-phenylbenzoylmethionine methyl ester

To a solution of 4-chlorosulfonyl-2-phenylbenzoyl methionine methyl ester from Example
5E in dichloromethane is added aqueous ammonia and the mixture is stirred until the
reaction is judged complete by TLC analysis. The organic phase is separated, dried and
evaporated and the product is purified by chromatography on silica gel.

Example 119B4-Isocyanatosulfonyl-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant sulfonamide from Example 119A in chlorobenzene is treated with
oxalyl chloride according to the procedure of Franz et al. (*J. Org. Chem.*, 1964, 29,
2592) to give the title compound.

Example 119C4-[(A-aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine methyl ester

5965 A mixture of the resultant isocyanate from Example 119B (1 equivalent) in dichloromethane is treated with 3-aminopyridine (1 equivalent) and stirred until the reaction is judged complete by tlc analysis. The solvent is evaporated and the product is purified by chromatography on silica gel.

Example 119D4-[(A-aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine

The resultant compound from Example 119C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 120A-NH-CO-NH-SO₂-B

5975 The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Example 5E to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5985 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 121A-NH-CO-NH-SO₂-CH₂-B

5990 The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 115A-C to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 122

A-O-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 27 with the exception that 3-hydroxypyridine is replaced by an alcohol from Table 6 (A-OH). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 123

A-O-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 124

A-O-CS-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂), (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 125

A-O-SO-NH-B

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 126

A-O-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH,

1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 127

A-O-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 128

A-O-CS-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by

6110 removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6115 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6120 Example 129

A-O-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products
6125 derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The
6130 solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6135 Example 130

A-O-SO₂-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products
6140 derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring
6145 the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane

and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 131

A-S-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Example 13A. The resultant fluorides are reacted according to the procedure of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 132

A-S-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6185

Example 133

A-S-CS-NH-B

6190 The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂), (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring
6195 the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
6200 anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 134

A-S-SO-NH-B

6205 The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis
6210 step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.
6215 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 135A-S-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 136A-S-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 137A-S-CS-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the

exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH) and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 138

A-S-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 139

A-S-SO₂-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting

group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of
dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is
complete. The solvent is evaporated and the residue is purified by chromatography on silica
gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 140

A-O-B

The procedure of Example 6 is used with the exception that 4-amino-2-phenylbenzoyl
methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 3-
bromopyridine is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products
derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by
removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant
compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and
trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is
evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 141

A-S-B

The procedure of Example 12 is used with the exception that 4-amino-2-phenylbenzoyl
methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 2-
chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-
I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is
followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring
the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane
and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The
solvent is evaporated and the residue is purified by chromatography on silica gel.

6330 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6335 Example 142

A-NH-B

The procedure of Example 24 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 2-bromopyridine hydrobromide is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I).
6340 For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The
6345 solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6350 Example 143

A-O-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 28 with the
6355 exception that 3-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of
6360 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
6365 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 144A-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 145A-C≡C-B

The procedure of Example 47 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 4-bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 146A-CH=CH-B

The products from Example 145 are reacted according to the procedure of Example 48.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 147

A-CH₂-CH₂-B

The products from Example 146 are reacted according to the procedure of Example 49.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 148

A-CO-C \equiv C-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 50 with the exception that 4-bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-230 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 149

A-CO-CH=CH-B

The products from Example 148 are reacted according to the procedure of Example 48.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to

prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 150

A-CO-CH₂-CH₂-B

The products from Example 149 are reacted according to the procedure of Example 49.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 151

A-SO₂-B

The anilines from Table 1, entries 28-132 (B-NH₂) are reacted according to the procedures of Example 13A. The resultant fluorides are reacted according to the procedure of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from Table 7 (A-SH). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 152

A-CH₂SO₂-B

The procedure of Example 12 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1, entries 28-132 (B-NH₂) and 2-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting

group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6480 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

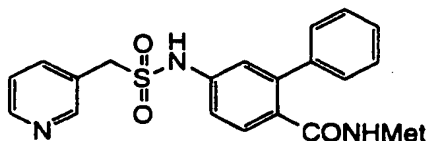
6485

Example 153

A-SO₂-CH₂-B

The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of
6490 Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of
6495 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
6500 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



Example 154

6505 {4-[(3-sulfonylmethyl)pyridyl]amino}-2-phenylbenzoyl}methionine

Example 154A

{4-[(3-sulfonylmethyl)pyridyl]amino}-2-phenylbenzoyl}methionine methyl ester

A mixture of 3-chlorosulfonylmethylpyridine hydrochloride (1.0 equivalent) and (4-amino-2-phenylbenzoyl)methionine methyl ester (1.0 equivalent) in dichloromethane is treated with triethylamine (2.2 equivalents). When judged complete by TLC analysis, the reaction is diluted with ethyl acetate, and then is washed with pH 4 water, saturated NaHCO₃, and brine. The mixture is dried and concentrated to give the crude title compound which is purified by chromatography on silica gel.

Example 154B

{4-[(3-sulfonylmethylpyridyl)amino]-2-phenylbenzoyl}methionine

The resultant compound from Example 154A is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 155

A-CH₂SO₂-NH-B

The procedure of Example 154 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 3-chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 (A-SO₂Cl).

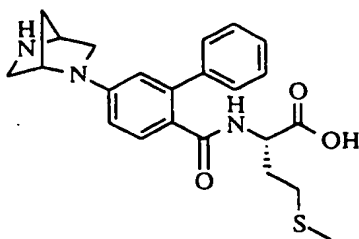
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 156

A-SO₂-NH-CH₂-B

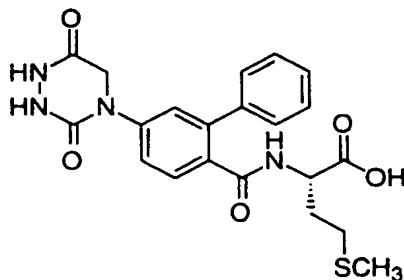
The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 154 with the exception that 3-chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 (A-SO₂Cl).

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

**Example 173****6545** [4-((2S,5S)-1,4-diazabicyclo(2.2.1)octan-1-yl)-2-phenylbenzoyl]methionine hydrochloride

To a solution of 74mg (0.13 mmol) of 2-phenyl-4-[(2S,5S)-4-Boc-1,4-diazabicyclo(2,2,1)octan-1-yl]benzoylmethionine methyl ester, prepared as in Example 172A, in 5 ml of THF was added 0.4 ml (0.4 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 2 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 60 mg of the resulting free acid as a oily residue. To a 2 ml of a 1:1 solution of TFA and dichloromethane was added 60 mg of the acid. After 30 min, The reaction mixture was thoroughly evaporated in high vacuum to give an oily residue. The residue was triturated with 0.3 ml of 3 M anhydrous HCl-ether in 5 ml of ether and the white solid was collected by filtration to give 43 mg (66 %) of [4-((2S,5S)-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine hydrochloride: HPLC 95% (purity); ¹H NMR (300 MHz, CD₃OD) δ 7.49-7.36 (m, 6H), 6.73 (dd, 1H, J=2.2, 8.4 Hz), 6.60 (d, 1H, J=2.1 Hz), 4.77 (s, 1H), 4.50 (m, 12H), 3.73 (m, 2H), 3.32 (m, 2H), 2.31-1.85 (m, 6H); ¹³C NMR (CD₃OD) δ 175.0, 173.1, 148.5, 143.7, 142.4, 131.4, 129.9, 129.6, 128.8, 126.6, 115.5, 112.4, 59.7, 56.8, 53.6, 53.2, 51.8, 37.1, 31.9, 31.1, 15.8.

6565



Example 224[4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionineExample 224A(4-carboxymethylamino-2-phenylbenzoyl)methionine methyl ester

6570 A mixture of (4-amino-2-phenylbenzoyl)methionine methyl ester (compound 8, 1.51 g, 4.21 mmol), glyoxylic acid monohydrate (466 mg, 5.06 mmol), sodium cyanoborohydride (1.0 M in THF, 4.2 mL), sodium acetate (0.5 g) and acetic acid (0.5 mL) in methanol (10 mL) was stirred for 14 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with saturated aqueous potassium dihydrogenphosphate, water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate, then 3% methanol-ethyl acetate) to give (4-carboxymethylamino-2-phenylbenzoyl)methionine methyl ester (1.46 g, 83%). ¹H NMR (300 MHz, CDCl₃) δ 7.67 (d, 1H), 7.39 (m, 5H), 6.54 (dd, 1H), 6.45 9d, 1H), 5.96 (br d, 1H), 4.63 (m, 1H), 3.88 (d, 2H), 3.67 (s, 3H), 2.04 (m, 2H), 2.00 (s, 3H), 1.86 (m, 1H), 1.67 (m, 1H). MS (APCI⁺) m/e 417 (M+H)⁺.

Example 224B

6585 [4-(*N*-tert-butoxycarbonylamino)carboxamidomethylamino-2-phenylbenzoyl]methionine methyl ester

6590 A mixture of the (4-carboxymethylamino-2-phenylbenzoyl)methionine methyl ester prepared in Example 224A (1.04 g, 2.50 mmol), *tert*-butylcarbazate (661 mg, 5.0 mmol), 3-hydroxy 1,2,3-benzotriazin-4(3*H*)-one (489 mg, 3.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (576 mg, 3.0 mmol) in dichloromethane (10 mL) was stirred at room temperature for 15 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate) to give [4-(*N*-tert-butoxycarbonylamino)carboxamidomethylamino-2-phenylbenzoyl]methionine methyl ester (671 mg, 51%). ¹H NMR (300 MHz, CDCl₃) δ 8.16 (d, 1H), 7.69 (d, 1H), 7.40 (m, 5H), 6.64 (dd, 1H), 6.53 (d, 1H), 6.45 (m, 1H), 5.96 (br d, 1H), 4.63 (m, 1H), 3.97 (d, 2H), 3.67 (s, 3H), 2.99 (m, 4H), 2.06 (m, 2H), 2.00 (s, 3H), 1.88 (m, 1H), 1.68 (m, 1H), 1.46 (s, 9H). MS (APCI⁺) m/e 531 (M+H)⁺.

6600

Example 224C[4-(N-tert-butoxycarbonylamino)carboxamidomethyl-(N-chloroformyl)amino-2-phenylbenzoyl]methionine methyl ester

To a -78 °C solution of the [4-(N-tert-butoxycarbonylamino)carboxamidomethylamino-2-phenylbenzoyl]methionine methyl ester prepared in Example 224B (258 mg, 0.481 mmol) in dichloromethane (3 mL) was added phosgene (1.93 M in toluene, 0.38 mL, 0.74 mmol), followed by triethylamine (0.20 mL, 1.5 mmol). The reaction was then left to warm to ambient temperature over 14 hours. The reaction mixture was then filtered through silica gel (10 g), rinsed with ethyl acetate, and concentrated *in vacuo*. The residue was purified by column chromatography (40% ethyl acetate-hexane) to give [4-(N-tert-butoxycarbonylamino)carboxamidomethyl-(N-chloroformyl)amino-2-phenylbenzoyl]methionine methyl ester (171 mg, 60%). ¹H NMR (300 MHz, DMSO-d₆) δ 8.24 (d, 1H), 7.33 (m, 5H), 7.28 (d, 1H), 6.68 (m, 3H), 4.39 (m, 2H), 4.30 (m, 1H), 3.62 (s, 3H), 2.25 (m, 2H), 2.00 (s, 3H), 1.83 (m, 2H), 1.51 (s, 9H).

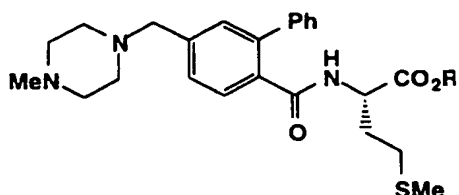
Example 224D[4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionine methyl ester

To a solution of the [4-(N-tert-butoxycarbonylamino)carboxamidomethyl-(N-chloroformyl)amino-2-phenylbenzoyl]methionine methyl ester prepared in Example 224C (70 mg, 0.118 mmol) in dichloromethane (2 mL) was added 2-mercaptoethanol (5 drops) and trifluoroacetic acid (1 mL). After 1.5 hour, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography (30% ethyl acetate-hexane) to give [4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionine methyl ester (43 mg, 80%). ¹H NMR (300 MHz, CDCl₃) δ 8.86 (br s, 1H), 8.69 (d, 1H), 7.40 (m, 5H), 6.69 (dd, 1H), 6.56 (d, 1H), 5.76 (br d, 1H), 4.63 (m, 1H), 4.32 (s, 2H), 3.65 (s, 3H), 2.99 (m, 4H), 2.09 (t, 2H), 2.01 (s, 3H), 1.89 (m, 1H), 1.68 (m, 1H). MS (CI⁺) m/e 457 (M+H)⁺.

6630

Example 224E[4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionine

The desired compound was prepared by saponification of the product of Example 224D using the procedure of Example 211. ¹H NMR (300 MHz, DMSO-d₆) δ 7.32 (m, 5H), 7.23 (d, 1H), 6.79 (d, 1H), 6.63 (dd, 1H), 6.56 (d, 1H), 6.38 (m, 1H), 4.00 (m, 1H), 3.50 (s, 2 H), 2.07 (m, 2H), 1.97 (s, 3H), 1.79 (m, 2H). MS (APCI⁺) m/e 465 (M+Na)⁺.



Example 289

[4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine

Example 289A

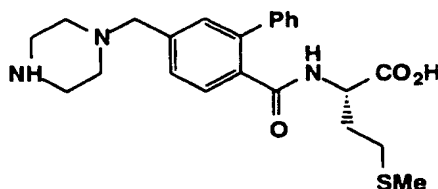
[4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine methyl ester

A solution of 4-chloromethyl-2-phenylbenzoic acid methyl ester (0.521 g, 2.00 mmol), prepared as in Example 286A, 1-methylpiperazine (0.607 g, 6.00 mmol), K₂CO₃ (0.663 g, 4.80 mmol), KI (0.332 g, 2.00 mmol), and Bu₄NBr (0.032 g, 0.10 mmol) in DMF (5 mL) was stirred for 2 hours at ambient temperature and then concentrated under reduced pressure. The residue was treated with a saturated LiOH-methanol (10 mL) and then heated at reflux for 5 hours. The mixture was concentrated and the residue was dissolved in H₂O. This solution was extracted with ethyl acetate (5x), and the aqueous phase was then acidified by the addition of 3 M HCl and lyophilized. The resulting white foam was dissolved in DMF (20 mL) and the solution was treated with L-methionine, methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.33 g, 8.00 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.56 g, 8.00 mmol), and N-methylmorpholine (1.23 g, 12.0 mmol). The reaction mixture was stirred at ambient temperature for 20 hours, diluted with ethyl acetate, and extracted with a 2:1 mixture of H₂O and saturated aqueous NaHCO₃ (2x), 1:1 mixture of the same (2x) and brine (2x). The organic phase was dried (MgSO₄) and concentrated to provide a gold oil. Radial chromatography (30% methanol-ethyl acetate) afforded the desired compound (0.321 g, 35%).

Example 289[4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine

6665 Saponification of the product of Example 289A using the procedure of Example 287D gave the desired compound as a white foam as the bis-hydrochloride, mono-sodium chloride. ¹H NMR (d₆-DMSO) δ 1.76-1.95 (comp, 2H), 2.00 (s, 3H), 2.17-2.36 (comp, 2H), 2.52 (br, 3H), 3.18-3.80 (br, 8H), 4.28-4.60 (br, 3H), 7.30-7.42 (comp, 3H), 7.47-7.55 (comp, 3H), 7.67-7.73 (m, 1H), 7.74-7.80 (br, 1H), 8.63 (d, *J* = 7.8 Hz, 1H).

6670 LRMS (CI): 442 (M+H)⁺.

Example 290

6675 (4-piperazinylmethyl-2-phenylbenzoyl)methionine

Example 290A4-*N*-tert-butoxycarbonylpiperazinylmethyl-2-phenylbenzoic acid

6680 A solution of 4-chloromethyl-2-phenylbenzoic acid methyl ester (0.521 g, 2.00 mmol), prepared as in Example 286A, piperazine (1.39 g, 16.0 mmol), K₂CO₃ (0.663 g, 4.80 mmol), KI (0.332 g, 2.00 mmol), and Bu₄NBr (0.032 g, 0.10 mmol) in DMF (7 mL) was stirred for 2 hours at ambient temperature and then concentrated under reduced pressure. The residue was treated with saturated LiOH-methanol (10 mL) and then heated at reflux for 5 hours. The mixture was concentrated and the residue was dissolved in H₂O.

6685 This solution was extracted with ethyl acetate (5x), and the aqueous phase was then acidified by the addition of 3 M HCl and lyophilized. The resulting white foam was dissolved in a 1:1 mixture of H₂O and 0.979 M NaOH (86 mL), and the solution was treated with *di*-*tert*-butyldicarbonate (6.68 g, 30.0 mmol). The reaction mixture was stirred at ambient temperature for 15 hours and then concentrated to remove THF. The mixture

6690 was treated with H₂O and saturated aqueous NaHCO₃ and then extracted with an ether (4x).

The aqueous phase was acidified to pH 3 by the addition of 3 M HCl and then extracted with 4:1 CHCl₃-methanol (10x). The combined organic extracts were dried twice with saturated aqueous Na₂SO₄ and concentrated to provide the desired compound (0.544 g, 69%) as an amber wax.

Example 290B

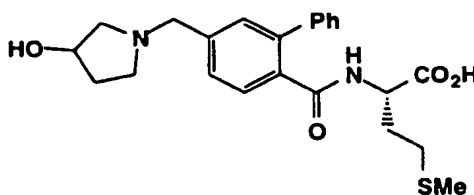
(4-*N*-*tert*-butoxycarbonylpiperazinylmethyl-2-phenylbenzoyl)methionine methyl ester

A solution of the product of Example 290A (0.544 g, 1.37 mmol), L-methionine, methyl ester hydrochloride (0.553 g, 2.74 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (1.14 g, 6.85 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.34 g, 6.85 mmol), and *N*-methylmorpholine (0.980 g, 9.59 mmol) in DMF (14 mL) was stirred at ambient temperature for 16 hours. The mixture was diluted with ethyl acetate and then extracted with a 2:1 mixture of H₂O and saturated aqueous NaHCO₃ (2x), a 1:1 mixture of the same (2x) and brine (2x). The organic phase was dried (MgSO₄) and concentrated to provide an amber oil. Radial chromatography (1:1 hexane-ethyl acetate) afforded the desired compound (0.356 g, 48%) as an amber oil.

Example 290C

(4-piperazinylmethyl-2-phenylbenzoyl)methionine

The desired compound was prepared from the product of Example 290B according to the method of Example 286E. ¹H NMR (300 MHz, DMSO-d₆) δ 1.75-1.96 (comp, 2H), 2.00 (s, 3H), 2.17-2.35 (comp, 2H), 3.3-3.7 (br, 8H), 4.28-4.38 (m, 1H), 4.28-4.38 (m, 1H), 4.38-4.54 (br, 2H), 7.30-7.44 (comp, 3H), 7.46-7.56 (comp, 3H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.76-7.82 (br, 1H), 8.66 (d, *J* = 7.7 Hz, 1H), 9.86-10.06 (br, 1H), 12.30-12.70 (br, 1H). LRMS (CI) *m/e* 248 (M+H)⁺.



Example 291

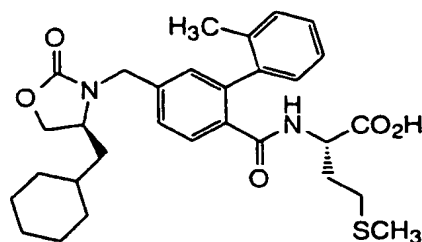
6720

[4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionineExample 291A[4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine methyl ester

A solution of 4-chloromethyl-2-phenylbenzoic acid methyl ester (0.521 g, 2.00 mmol), prepared as in Example 286A, 3-pyrrolidinol (0.178 g, 2.00 mmol), K₂CO₃ (0.553 g, 4.00 mmol), and Bu₄NI (0.0754 g, 0.20 mmol) in CH₃CN (5 mL) was stirred for 15 hours, treated with LiOH•H₂O (0.506 g, 12.0 mmol), and then heated at reflux for 5 hours. The solution was cooled to ambient temperature and added to a mixture of L-methionine methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.66 g, 10.00 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.96 g, 10.00 mmol), and triethylamine hydrochloride (2.81 g, 20 mmol) in CH₃CN (15 mL). After 12 days the mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The solution was extracted with a 1:1 mixture of H₂O and saturated aqueous NaHCO₃ (4x) and brine. The organic phase was dried (MgSO₄) and concentrated to provide a gold oil. Radial chromatography (12% methanol-ethyl acetate) afforded the desired compound (0.494 g, 56%).

Example 291B[4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine

Saponification of the product of Example 289A using the procedure of Example 287D gave the desired compound as a white foam as the bis-hydrochloride, mono-sodium chloride. ¹H NMR (300 MHz, DMSO-d₆) δ 1.77-2.06 (comp, 5H), 2.16-2.36 (comp, 2H), 2.94-3.04 (m, 1H), 3.12-3.34 (comp, 2H), 3.34-3.56 (comp, 2H), 4.28-4.37 (m, 1H), 4.37-4.60 (comp, 2H), 4.60-5.50 (br, 2H), 7.32-7.43 (comp, 3H), 7.45-7.56 (comp, 3H), 7.65-7.80 (comp, 2H), 8.68 (d, J = 7.8 Hz, 1H), 11.2-11.9 (m, 1H). LRMS (CI) m/e 429 (M+H)⁺.

Example 349

[4-(5-cyclohexylmethyloxazolid-2-on-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

Example 349A

[4-(1-hydroxy-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

6755 A mixture of [4-formyl-2-(2-methylphenyl)benzoyl]methionine ethyl ester (614 mg, 1.54 mmol), prepared according to Example 158F except substituting [4-hydroxymethyl-2-(2-methylphenyl)benzoic acid for 4-hydroxymethyl-2-phenylbenzoic acid in Example 158E, (S)-(+)-2-amino-3-cyclohexyl-1-propanol hydrochloride (357 mg, 1.84 mmol) and diisopropylethylamine (0.135 mL, 0.77 mmol) in toluene was refluxed for 5 hours using a
6760 Dean-Stark apparatus. The reaction mixture was cooled to ambient temperature and diluted with ethanol. Sodium cyanoborohydride (145 mg) and o-bromocresol green was added. The reaction mixture was stirred while acidity was maintained using HCl-ethanol. The reaction was quenched with saturated aqueous potassium carbonate and the mixture was extracted with dichloromethane (2x). The combined organic layers were dried over
6765 magnesium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel (5% methanol-chloroform) gave the desired compound (840 mg).

Example 349B

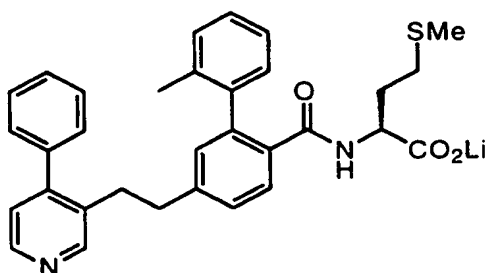
[4-(1-hydroxy-3-cyclohexylprop-2-yl-N-ethoxycarbonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

6770

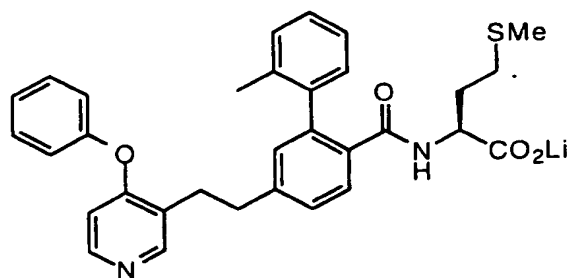
To a solution in THF of the product of Example 348A (173 mg, 0.32 mmol) and diisopropylethylamine (66 μ L, 0.38 mmol) was added ethyl chloroformate (40 μ L, 0.38 mmol) and the reaction mixture was stirred for 1.5 hours at ambient temperature. The reaction mixture was poured into ethyl acetate and the organic phase was washed with
6775 aqueous 2N HCl, dried over magnesium sulfate, filtered, and concentrated in vacuo to give the desired compound as a clear oil which was used without further purification.

Example 349C[4-(5-cyclohexylmethyl-2-oxazolidon-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

6780 To a 100 °C solution of the product of Example 348B in toluene was added sodium
ethoxide (21% in ethanol, 30 μ L) and the reaction mixture was stirred for 10 minutes. The
reaction mixture was cooled to ambient temperature and diluted with saturated aqueous
ammonium chloride. The mixture was extracted with ethyl acetate. The organic phase was
6785 dried over magnesium sulfate, filtered, and concentrated in vacuo. Chromatography on
silica gel (33% ethyl acetate-hexane) gave the title compound as the ethyl ester.
Saponification of the ethyl ester using lithium hydroxide gave the title compound. ^1H NMR
(DMSO- d_6 , 300 MHz) δ 8.13 (m, 1H), 7.41 (d, J = 7 Hz, 1H), 7.25 (d, J = 7 Hz, 1H),
7.11-7.02 (m, 4H), 4.45 (d, J = 15 Hz, 1H), 4.34 (dd, J = 9, 8 Hz, 1H), 4.19 (d, J = 15
Hz, 1H), 4.10 (m, 1H), 3.84 (dd, J = 8, 8 Hz, 1H), 3.58 (m, 1H), 2.10-1.83 (m, 5H),
6790 1.85 (s, 3H), 1.47-1.37 (m, 8H), 1.10-0.92 (m, 5H), 0.85-0.57 (m, 2H). MS (DCI-
NH $_3$) m/e 539 ($M+H$) $^+$, 556 ($M+NH_4$) $^+$.

Example 452N-[4-(2-(2-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

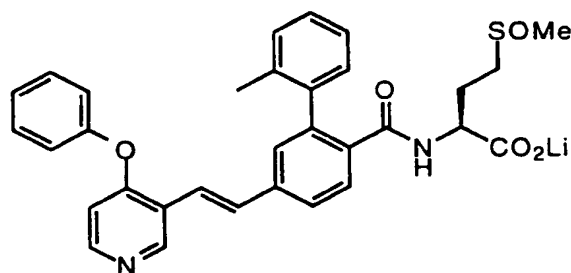
6795 The desired compound was prepared according to the method of Examples 210 - 212
 ^1H nmr (300 MHz, DMSO- d_6): δ 7.2-7.04 (m, 15 H), 6.89 (dd, 1 H), 6.54 (br d, 1 H),
4.12 (m, 1 H), 2.81 (t, 2 H), 2.63 (t, 2 H), 2.00 (m, 1 H), 1.88-1.87 (br s, 6 H), 1.73 (m,
6800 2 H), 1.56 (m, 1 H). MS (ESI $-$): m/e 522 ($M-H$) $^-$.

**Example 453**

6805 N-[4-(2-(2-phenoxyphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 and 211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.88 (br d, 1 H), 7.55 (m, 2 H), 7.40-7.17 (m, 11 H), 7.10 (t, 1 H), 6.96 (m, 4 H), 3.65 (m, 1 H), 2.15 (m, 1 H), 2.00 (m, 1 H), 1.91 (br s, 6 H), 1.75-1.55 (m, 2 H). MS (APCI -): m/e 536 (M-H)⁻.

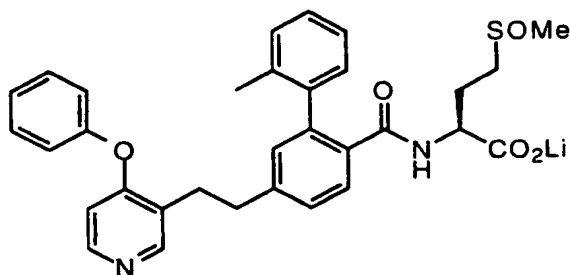
6810

**Example 454**

6815 N-[4-(2-(2-phenoxyphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid lithium salt

The desired compound was prepared according to the method of Examples 210 and 211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.88 (br d, 1 H), 7.62-7.50 (m, 2 H), 7.40-7.17 (m, 11 H), 7.10 (t, 1 H), 6.98 (m, 4 H), 3.90 (m, 1 H), 2.45 (s, 3 H), 2.39, 2.36 (2 s's, 3 H), 2.10-1.64 (m, 4 H). MS (ESI -): m/e 552 (M-H)⁻.

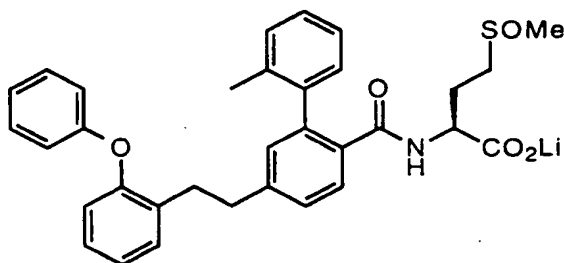
6820



Example 455N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

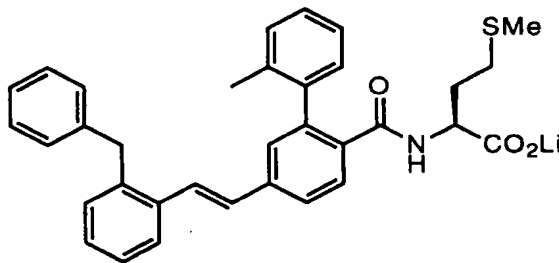
6825 The desired compound was prepared according to the method of Examples 210 - 212.. ¹H nmr (300 MHz, DMSO-d₆): δ 7.45-6.90 (m, 17 H), 3.65 (m, 1 H), 2.88 (br s, 4 H), 2.18-2.00 (m, 2 H), 1.91 (br s, 6 H), 1.70-1.50 (m, 2 H). MS (APCI -): m/e 538 (M-H)⁻.

6830

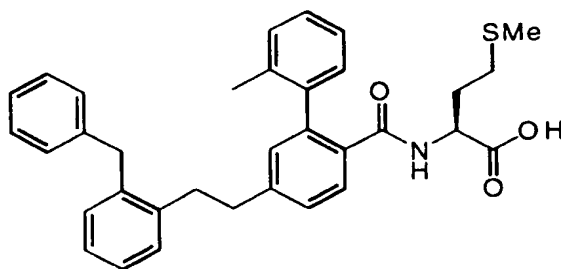
Example 456N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid lithium salt

6835 The desired compound was prepared according to the method of Examples 210 - 212.. ¹H nmr (300 MHz, DMSO-d₆): δ 7.43 (m, 1 H), 7.34 (m, 3 H), 7.25-7.00 (m, 9 H), 6.95 (m, 1 H), 6.85 (m, 3 H), 3.90 (m, 1 H), 2.88 (br s, 4 H), 2.41-2.37 (4 s's, 6 H), 2.10-1.64 (m, 4 H). MS (ESI -): m/e 554 (M-H)⁻.

6840

Example 457N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

6845 The desired compound was prepared according to the method of Examples 210 and 211.. ¹H nmr (300 MHz, DMSO-d₆): δ 7.70 (m, 1 H), 7.59 (m, 1 H), 7.51 (m, 2 H), 7.34-7.10 (m, 14 H), 6.96 (br s, 1 H), 4.17 (br s, 2 H), 3.63 (m, 1 H), 2.19 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI -): m/e 534 (M-H)⁻.

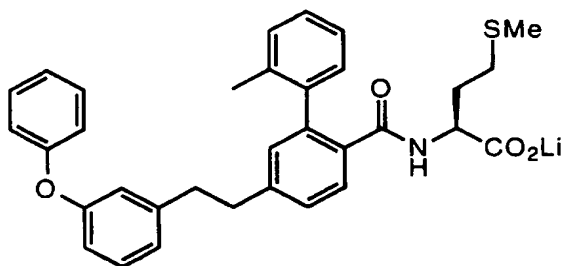


6850

Example 458**N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): δ 7.60-7.40 (m, 3 H), 7.25-7.07 (m, 12 H), 7.00-6.80 (m, 2 H), 3.97 (s, 2 H), 3.61 (m, 1 H), 2.83 (m, 2 H), 2.72 (m, 2 H), 2.08 (m, 1 H), 1.97 (m, 1 H), 1.96, 1.91 (2 br s's, 6 H), 1.80-1.52 (m, 2 H). MS (APCI -): m/e 536 (M-H)⁻.

6855

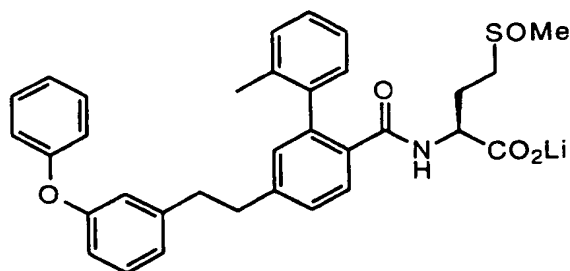


6860

Example 459**N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): δ 7.44 (d, 1 H), 7.35 (tt, 2 H), 7.25 (dt, 1H), 7.19 (m, 4 H), 7.10 (tt, 2 H), 6.98 (dt, 1 H), 6.96-6.83 (m, 5 H), 6.79 (ddd, 1 H), 3.64 (m, 1 H), 2.91 (br s, 4 H), 2.08 (m, 1 H), 1.95 (m, 1 H), 1.91 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI -): m/e 538 (M-H)⁻.

6865



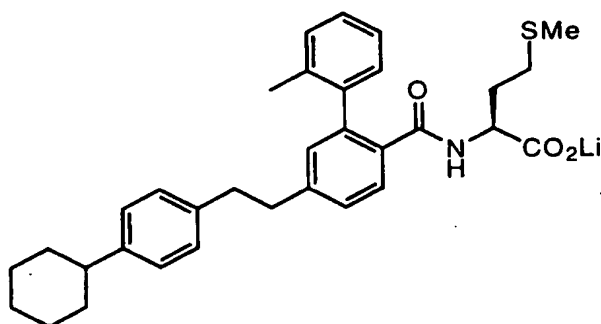
6870

Example 460**N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfanylbutanoic acid lithium salt**

The desired compound was prepared according to the method of Examples 210 -

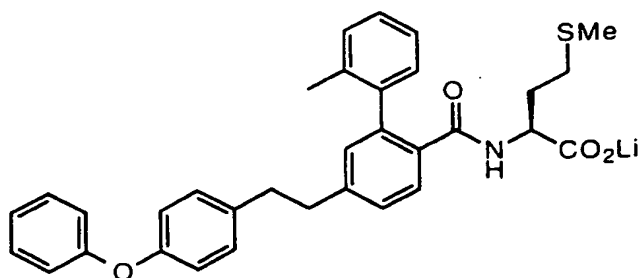
6875 212.. ¹H nmr (300 MHz, DMSO-d₆): 7.44 (dd, 1 H), 7.35 (tt, 2 H), 7.25 (dt, 1 H), 7.19 (m, 4 H), 7.10 (tt, 2 H), 6.98 (dt, 1 H), 6.96-6.83 (m, 5 H), 6.79 (ddd, 1 H), 3.90 (m, 1 H), 2.91 (br s, 4 H), 2.45 (s, 3 H), 2.39, 2.36 (2 s's, 3 H), 2.20-1.54 (m, 4 H). MS (ESI -): m/e 554 (M-H)⁻.

6880

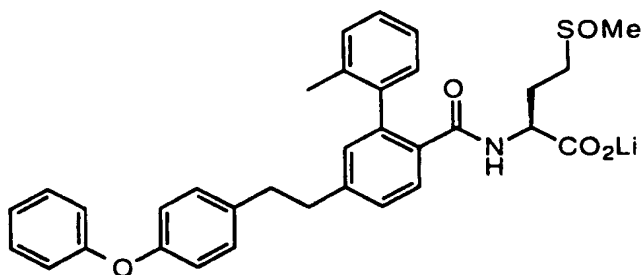
**Example 461****N-[4-(2-(4-cyclohexylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 -

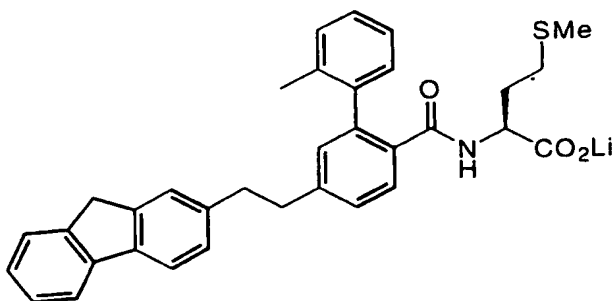
6885 212.. ¹H nmr (300 MHz, DMSO-d₆): δ 7.45 (d, 1 H), 7.29 (dd, 1 H), 7.25-7.05 (m, 8 H), 6.88 (m, 2 H), 3.64 (m, 1 H), 2.88 (m, 4 H), 2.44 (m, 1 H), 2.10-1.30 (m, 14 H), 1.91 (br s, 6 H). MS (APCI -): m/e 528 (M-H)⁻.

**Example 462****N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): 7.45 (d, 1 H), 7.40-7.27 (m, 3 H), 7.25-7.12 (m, 7 H), 7.10 (tt, 1 H), 6.98-6.87 (m, 5 H), δ 3.67 (m, 1 H), 2.91 (br s, 4 H), 2.16-1.95 (m, 2 H), 1.91 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI -): m/e 538 (M-H)⁻.

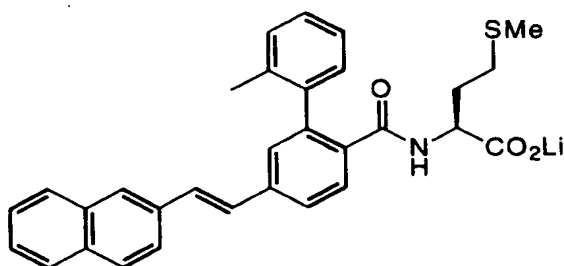
**Example 463****N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid lithium salt**

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): 7.66-6.87 (m, 17 H), 3.70 (m, 1 H), 2.92 (br s, 4 H), 2.40-2.37 (4 s's, 6 H), 2.20-1.54 (m, 4 H). MS (ESI -): m/e 554 (M-H)⁻.

**Example 464****N-[4-(2-fluoren-4-ylethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

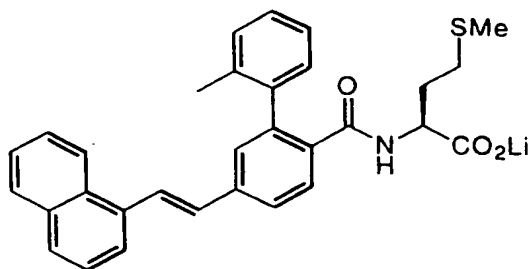
The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): δ 7.84 (d, 1 H), 7.77 (d, 1 H), 7.56 (d, 1 H), 7.45 (d, 1 H), 7.44 (s, 1 H), 7.40-6.86 (m, 10 H), 3.86 (s, 2 H), 3.64 (m, 1 H), 2.98 (br s, 4 H), 2.08 (m, 1 H), 1.95 (m, 1 H), 1.91 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI -):

m/e 538 (M-H)⁻.

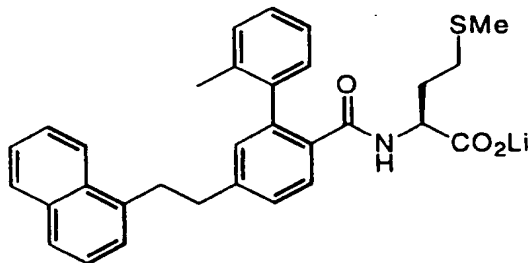
**Example 465****N-[4-(2-naphth-2-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Examples 210 and 211. ¹H nmr (300 MHz, CDCl₃): δ: δ 8.07 (dd, 1 H), 7.90-7.80 (m, 4 H), 7.74 (dd, 1 H), 7.66 (dd, 1 H), 7.51 (m, 2 H), 7.42-7.31 (m, 6 H), 7.25 (m, 1 H), 5.94 (t, 1 H), 4.60 (m, 1 H), 2.20-2.00 (4 s's, 6 H), 2.12 (m, 1 H), 2.03 (m, 1 H), 1.94 (m, 1 H), 1.58 (m, 1

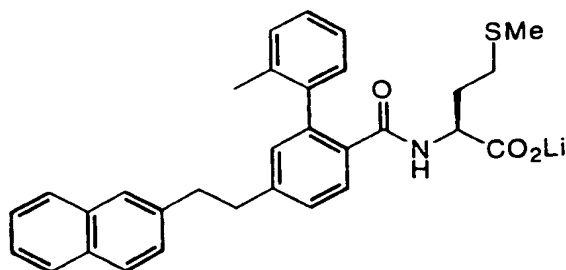
H). MS (CI +): m/e 496 (M+H)⁺.

**Example 466****N-[4-(2-naphth-1-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

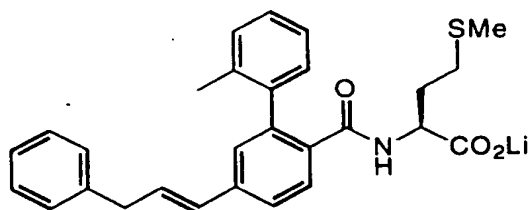
The desired compound was prepared according to the method of Examples 210 and 211. ¹H nmr (300 MHz, MeOD-d₄): δ 8.28 (d, 1 H), 8.12 (dd, 1 H), 7.90-7.72 (m, 5 H), 7.63-7.42 (m, 5 H), 7.35-7.10 (m, 5 H), 4.25 (m, 1 H), 2.98 (br s, 4 H), 2.30 (m, 1 H), 2.10 (m, 1 H), 2.02-1.97 (4 s's, 6 H), 1.84 (m, 1 H), 1.68 (m, 1 H). MS (ESI -): m/e 494 (M-H)⁻.

**Example 467****N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

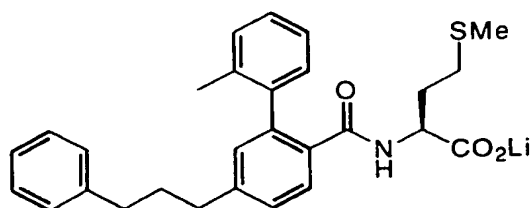
The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, MeOD-d₄): δ 8.08 (d, 1 H), 7.85 (dd, 1 H), 7.70 (d, 1 H), 7.63-7.38 (m, 4 H), 7.37-7.15 (m, 6 H), 7.05-6.83 (m, 2 H), 4.24 (m, 1 H), 3.42 (t, 2 H), 3.12 (t, 2 H), 2.27-2.05 (m, 2 H), 2.00 (br s, 6 H), 1.90-1.60 (m, 2 H). MS (ESI -): m/e 496 (M-H)⁻.

**Example 468****N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, MeOD-d₄): δ 7.66 (m, 3 H), 7.45 (m, 2 H), 7.31 (m, 2 H), 7.24 (dd, 1 H), 7.20 (dd, 1 H), 7.13-7.00 (m, 4 H), 6.80 (br d, 1 H), 4.13 (m, 1 H), 3.01 (t, 4 H), 1.91, 1.88, 1.81 (3 br s's, 6 H), 1.95-1.48 (m, 4 H). MS (ESI -): m/e 496 (M-H)⁻.

**Example 469****N-[4-(3-phenylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine
(1:1 mixture of olefin isomers)**

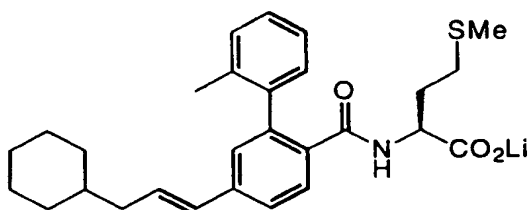
The desired compound was prepared according to the method of Examples 210 and 211. ¹H nmr (300 MHz, CDCl₃): δ 8.00, 7.96 (2 d's, from each of the isomers, 1 H), 7.48-7.08 (11 H), 6.52-6.30 (m, 2 H), 5.88 (m, 1 H), 4.56 (m, 1 H), 3.60 (2 d's, from each of the isomers, 2 H), 2.20-2.00 (m, 8 H), 1.90 (M, 1 H), 1.52 (m, 1 H). MS (CI +) m/e 460 (M+H)⁺.

**Example 470**

6970 N-[4-(3-naphth-2-ylpropyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212.. ¹H nmr (300 MHz, MeOD-d₄): δ 7.68 (t, 1 H), 7.65 (t, 1 H), 7.51 (m, 2 H), 7.34-7.06 (m, 9 H), 6.93 (m, 1 H), 4.17 (m, 1 H), 2.73 (t, 2 H), 2.66 (t, 2 H), 1.96 (m, 1 H), 1.99 (m, 3 H), 1.97, 1.89 (2 br s's, 6 H), 1.72 (m, 1 H), 1.53 (m, 1 H). MS (ESI -): m/e 510 (M-H)⁻.

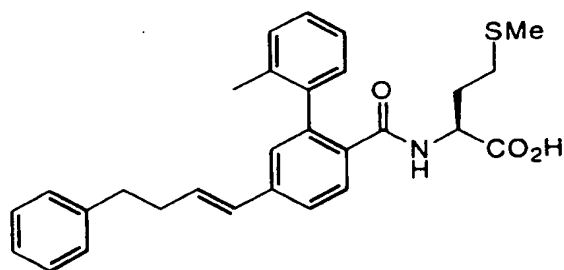
6975

**Example 471**

6980 N-[4-(3-cyclohexylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

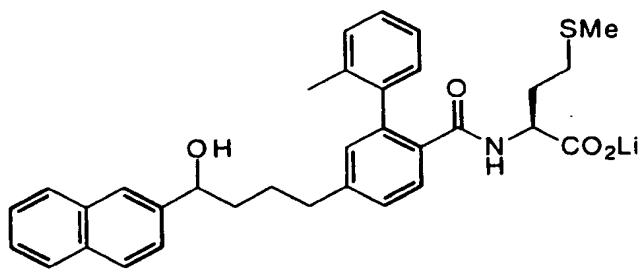
The desired compound was prepared according to the method of Examples 210 and 211.. ¹H nmr (300 MHz, DMSO-d₆): δ 7.46 (m, 2 H), 7.25-7.09 (m, 6 H), 6.96 (m, 1 H), 6.40 (m, 1 H), 3.64 (m, 1 H), 3.18 (m, 2 H), 2.2-2.05 (m, 2 H), 2.03-1.92 (3 br s's, 6 H), 1.75-0.90 (m, 13 H). MS (ESI -): m/e 464 (M-H)⁻.

6985

**Example 472****N-[4-(4-phenylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine**

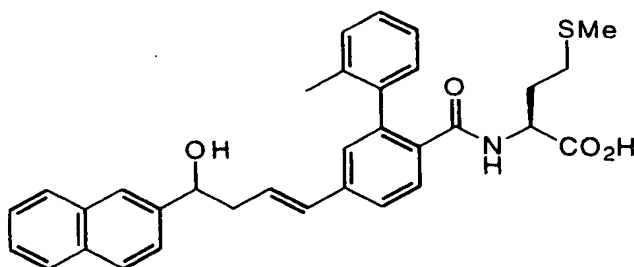
6990 The desired compound was prepared according to the method of Examples 210 and 211. ^1H nmr (300 MHz, CDCl_3): δ 7.98 (m, 1 H), 7.50-7.10 (m, 12 H), 6.41 (m, 1 H), 5.88 (m, 1 H), 4.57 (m, 1 H), 2.82 (m, 2 H), 2.57 (m, 2 H), 2.20-2.00 (m, 8 H), 1.92 (m, 1 H), 1.52 (m, 1 H). MS (CI +) m/e 474 ($\text{M}+\text{H}$) $^+$.

6995

**Example 473****N-[4-(4-naphth-2-ylbut-4-on-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

7000 The desired compound was prepared according to the method of Examples 210 - 212. ^1H nmr (300 MHz, $\text{DMSO}-d_6$): δ 8.61 (s, 1 H), 8.10 (br d, 1 H), 7.98 (m, 2 H), 7.63 (m, 2 H), 7.46 (m, 2 H), 7.31 (m, 1 H), 7.23-6.87 (m, 6 H), 3.44 (m, 1 H), 3.20 (m, 2 H), 2.75 (m, 2 H), 2.30-1.97 (m, 4 H), 1.95 (br s, 3 H), 1.91 (br s, 3 H), 1.90-1.56 (m, 2 H). MS (ESI -): m/e 538 ($\text{M}-\text{H}$) $^-$.

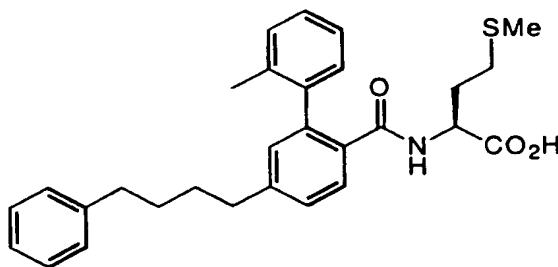
7005

**Example 474****N-[4-(4-naphth-2-ylbut-4-ol-1-enyl)-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Examples 210 and

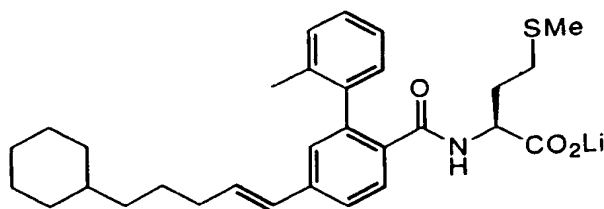
7010 211. ^1H nmr (300 MHz, DMSO- d_6): δ 7.95-7.83 (m, 4 H), 7.56 (dd, 1 H), 7.48 (m, 3 H), 7.43 (m, 1 H), 7.25-7.08 (m, 5 H), 7.00-6.85 (m, 1 H), 6.45 (m, 1 H), 4.86 (t, 1 H), 3.64 (m, 1 H), 2.63 (br t, 2 H), 2.17 (m, 1 H), 1.98, 1.91 (2 br s's, 6 H), 1.95 (m, 1 H), 1.90-1.56 (m, 2 H). MS (ESI $-$): m/e 538 ($M-H$) $^-$.

7015

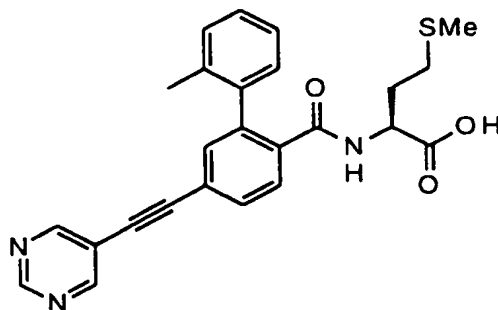
**Example 478****N-[4-(4-cyclohexylbutyl)-2-(2-methylphenyl)benzoyl]methionine sodium salt**

The desired compound was prepared according to the method of Examples 210 -

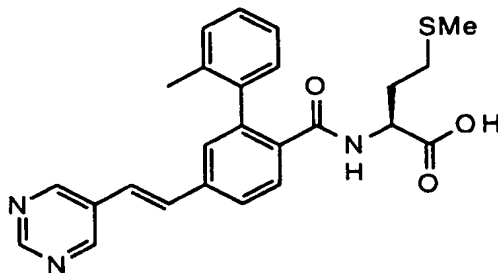
7020 212. ^1H nmr (300 MHz, DMSO- d_6): δ 7.45 (d, 1 H), 7.27-7.10 (m, 5 H), 6.96 (m, 1 H), 6.89 (br s, 1 H), 3.67 (m, 1 H), 2.62 (t, 2 H), 2.15 (m, 1 H), 1.98, 1.91 (2 br s's, 6 H), 1.97 (m, 1 H), 1.70-0.75 (m, 19 H). MS (ESI $-$): m/e 480 ($M-H$) $^-$.

**Example 480****N-[4-(5-phenylpent-1-enyl)-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Examples 210 and 211. ^1H nmr (300 MHz, CDCl_3): δ 8.00 (tt, 1 H), 7.43 (dt, 1 H), 6.38-7.15 (m, 11 H), 6.39 (m, 1 H), 5.85 (m, 1 H), 4.52 (m, 1 H), 2.70 (m, 2 H), 2.19 (m, 1 H), 2.20-2.00 (4 s's, 6 H), 2.10 (m, 3 H), 1.90-1.50 (m, 4 H). MS (CI +): m/e 488 (M+H) $^+$.

**Example 493****N-[4-(2-pyrimidin-5-ylethynyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 - 211. ^1H nmr (300 MHz, $\text{DMSO}-d_6$): δ 9.20 (s, 1 H), 9.04 (s, 2 H), 7.63 (m, 3 H), 7.42 (m, 1 H), 7.30-7.18 (m, 4 H), 7.16-7.00 (m, 2 H), 3.48 (m, 1 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H).

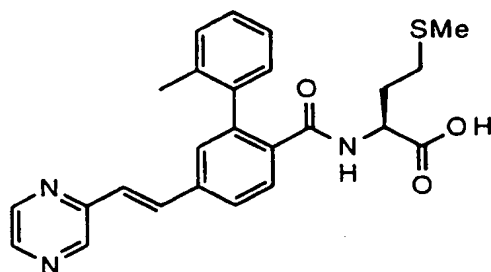
**Example 494**

7045

N-[4-(2-pyrimidin-5-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211
¹H nmr (300 MHz, DMSO-d₆): δ 9.06 (s, 1 H), 9.04 (s, 2 H), 7.67 (br d, 1 H), 7.00 (m, 2 H), 7.47 (m, 1 H), 7.38 (d, 1 H), 7.30-7.15 (m, 3 H), 7.10-6.97 (m, 2 H), 3.66 (m, 1 H), 2.20 (m, 1 H), 2.03 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -):
 m/e 446 (M-H)⁻.

7050

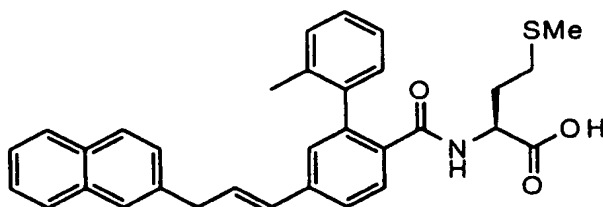
Example 495

7055

N-[4-(2-pyrazin-2-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211
¹H nmr (300 MHz, DMSO-d₆): δ 8.78 (s, 1 H), 8.63 (dd, 1 H), 8.51 (d, 1 H), 7.82 (d, 1 H), 7.76 (dd, 1 H), 7.59 (d, 1 H), 7.52 (m, 2 H), 7.30-7.10 (m, 4 H), 7.02 (m, 1 H), 3.68 (m, 1 H), 2.20 (m, 1 H), 2.03 (m, 1 H), 1.93 (br s, 16 H), 1.70 (m, 1 H), 1.58 (m, 1 H).
 MS (ESI -): m/e 446 (M-H)⁻.

7060

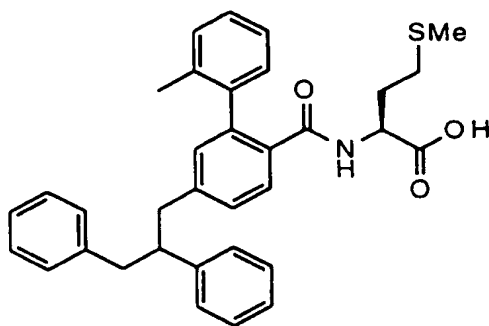
Example 496

7065

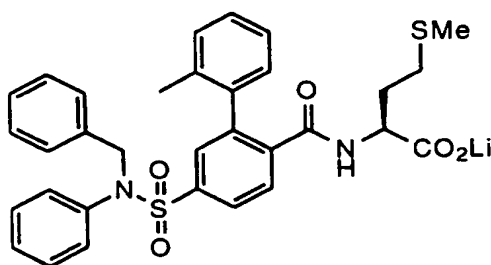
N-[4-(3-naphth-2-ylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt(1:1 mixture of olefin isomers)

The desired compound was prepared according to the method of Examples 210 - 211
¹H nmr (300 MHz, MeOD-d₄): δ 7.85-7.58 (m, 5 H), 7.51-7.36 (m, 4 H), 7.32-7.10 (m, 5 H), 6.61 (m, 1 H), 4.24 (m, 1 H), 3.72, 3.67 (2 d's, 2 H, 1:1 ratio), 2.24 (m, 1 H), 2.08-
 1.95 (4 s's, 6 H), 1.99 (m, 1 H), 1.90-1.60 (m, 2 H). MS (ESI -) m/e 508 (M-H)⁻.

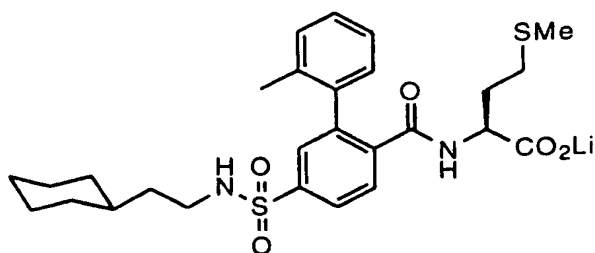
7070

**Example 572****N-[4-(2,3-diphenylpropan-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

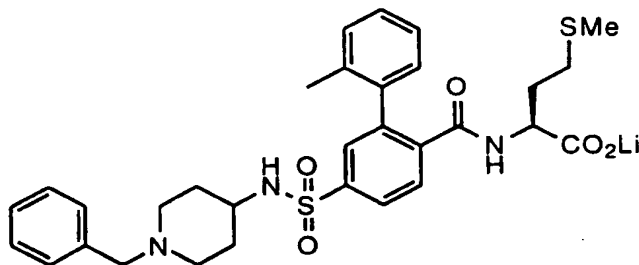
The desired compound was prepared according to the method of Examples 210 - 212 (DMSO-d₆) δ 7.38 (d, 1H), 7.10, 6.90, 6.73 (all m, total 17H), 3.75 (m, 1H), 2.98 (m, 5H), 2.10-1.50 (envelope, 10H). MS (ESI) 536 (M-H)⁻. Anal calcd for C₃₄H₃₄LiNO₃S · 0.25 H₂O: C, 74.50; H, 6.34; N, 2.56. Found: C, 7.10; H, 5.95; N, 2.53.

**Example 768****N-[4-(N-Benzyl-N-phenylaminosulfonyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Example 5E. ¹H (d₆-DMSO): δ 7.7-7.9 (4H, m); 7.3-7.1 (13H, m); 4.84 (2H, s); 4.1 (1H, m) 3.2 (3H, s); 1.9 (3H, s); 2.1-1.6 (4H, m). ESI(-)/MS: 587 (M-Li)

Example 772N-[4-(N-2-cyclohexylethylaminosulfonyl)-2-phenylbenzoyl]methionine lithium salt

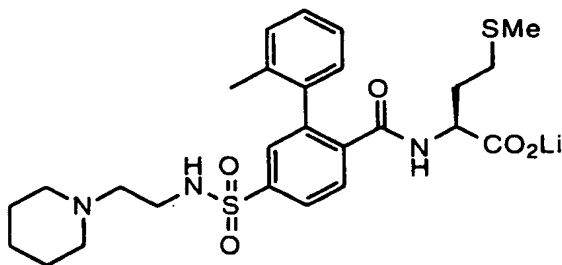
7095 The desired compound was prepared according to the method of Example 5E. ¹H (CD₃OD): 7.85-7.9 (1H, d); 7.7-7.8 (1H, d); 7.6-7.7 (1H, s); 7.2-7.3 (4H, m); 4.2-4.3 (1H, m); 2.8-2.9 (2H, t); 2.05-2.1 (2H, m); 2.0 (3H, s); 1.9 (3H, s); 1.6-1.7 (6H, m) 1.1-1.4 (7H, m); 1.7-1.86 (2H, m). ESI(-)/MS: 521(M-Li); 487, 459.



7100

Example 773N-[4-(1-benzylpiperidin-4-ylaminosulfonyl)-2-phenylbenzoyl]methionine lithium salt

7105 The desired compound was prepared according to the method of Example 5E. ¹H (CD₃OD): 7.82-7.94 (1H, d); 7.75-7.81 (1H, d); 7.62-7.72 (1H, s); 7.1-7.38 (9H, m); 4.2-4.3 (1H, m); 3.1(2H, s); 3.0-3.1 (1H, m); 2.7-2.8 (2H, d); 2.42-2.54 (2H, t); 1.78-2.3 (11H, m); 1.6-1.78 (3H, m); 1.4-1.6 (2H, m). ESI(-)/MS: 594(M-Li).

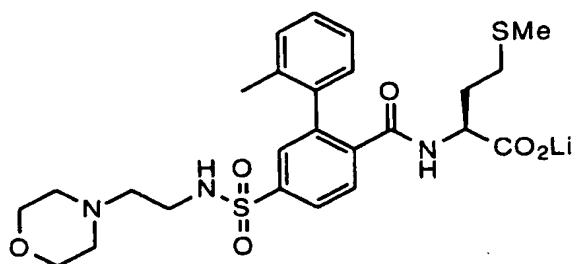


7110

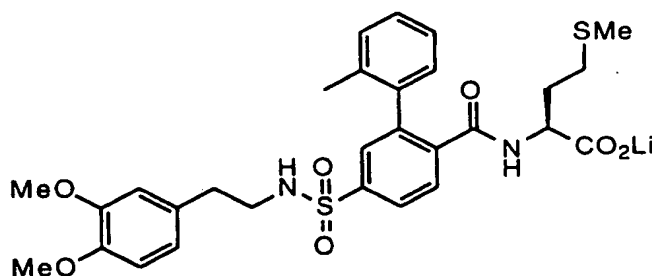
Example 774

N-[4-*N*-(2-piperidin-1ylethyl)aminosulfonyl]-2-phenylbenzoyl]methionine lithium salt

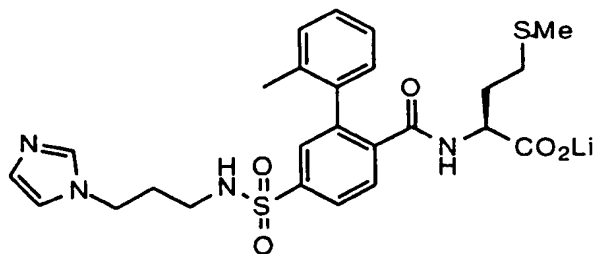
The desired compound was prepared according to the method of Example 5E. ¹H (CD₃OD): 7.82-7.94 (1H, d); 7.75-7.81 (1H, d); 7.62-7.72 (1H, s); 7.1-7.38 (4H, m); 4.18-4.3 (1H, m); 3.1(2H, m); 2.34-2.5 (5H, m); 2.2-2.35 (2H, m); 2.05-2.2 (2H, m); 1.93-2.05 (3H, s); 1.8-1.95 (4H, m); 1.6-1.7 (2H, m); 1.55-1.6 (3H, m); 1.4-1.5 (2H, m). ESI(-)/MS: 532 (M-Li); 488; 357.

Example 775*N*-[4-*N*-(2-morpholin-1ylethyl)aminosulfonyl]-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 5E. ¹H (CD₃OD): 7.9-8.1 (1H, d); 7.8-7.9 (1H, d); 7.67-7.8 (1H, s); 7.1-7.4 (4H, m); 4.2-4.3 (1H, m); 3.4-3.7 (4H, m); 3.4-3.2 (4H, m); 2.9-3.2 (2H, t); 1.6-2.6 (12H, m) ESI(-)/MS: 534(M-Li); 490; 462.

Example 776*N*-[4-(2-(3,4-dimethoxyphenyl)ethyl)aminosulfonyl]-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 5E. ¹H(MeOH-*d*₄): δ 7.78-7.9 (2H, m); 7.62-7.7 (1H,s); 7.1-7.3 (4H, m); 6.78-6.82 (1H, d); 6.72-6.78 (1H, d); 6.65-6.72 (1H, q); 4.2-4.3 (1H, m); 3.75-3.8 (6H, s); 3.08-3.18 (2H, m); 2.58-2.7 (2H, t); 1.6- 2.26 (10H, m). ESI(-)/MS: 585(M-Li); 541; 410.

**Example 777**

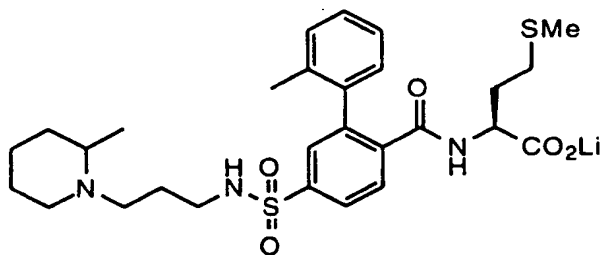
N-[4-(3-imidazol-1-ylpropylaminosulfonyl)-2-phenylbenzoyl]methionine lithium salt

7140

The desired compound was prepared according to the method of Example 5E.

^1H (MeOH- d_4): δ 7.78-7.9 (2H, dd); 7.5-7.6 (2H, m); 7.1-7.3 (4H, m); 7.1 (1H, s); 6.92 (1H, s); 4.2-4.3 (1H, m); 4.05-4.18 (2H, t); 2.8-2.9 (2H, t); 1.6-2.3 (12H, m). ESI(-)/MS: 529(M-Li); 281; 255.

7145

**Example 778**

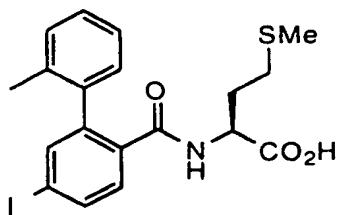
N-[4-(3-(2-methylpiperidin-1-yl)propylaminosulfonyl)-2-phenylbenzoyl]methionine lithium salt

7150

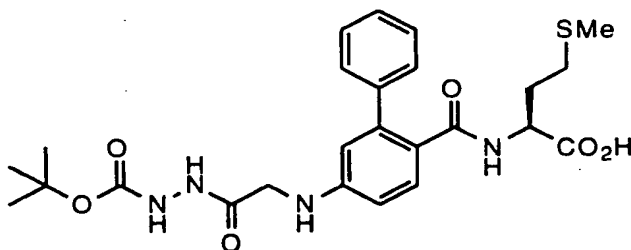
The desired compound was prepared according to the method of Example 5E.

^1H (MeOH- d_4): δ 7.8-7.94(2H, dd); 7.6-7.7 (1H, s); 7.1-7.4 (4H, m); 4.2-4.3 (1H, m); 2.84-2.94 (2H, t); 2.7-2.87 (2H, m); 1.8- 2.5 (13H, m); 1.4-1.8 (6H, m); 1.24-1.349 (2H, m); 1.0-1.1 (3H, m). ESI(-)/MS: 560(M-Li); 385; 281.

7155

**Example 783****N-[4-iodo-2-(2-methylphenyl)benzoyl]methionine**

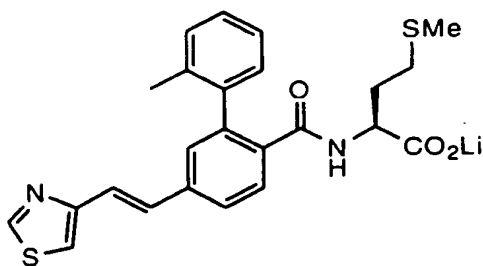
7160 The desired compound was prepared according to the method of Example 210C. ¹H nmr (300 MHz, CDCl₃): δ 7.83 (dd, 1 H), 7.72 (dd, 1 H), 7.60 (s, 1 H), 7.39-7.16 (m, 4 H), 5.89 (m, 1 H), 4.58 (m, 1 H), 2.20-2.00 (m, 8 H), 1.96 (m, 1 H), 1.58 (m, 1 H). MS (CI +) m/e 452 (M+H)⁺.



7165

Example 784**N-[4-N-(t-Butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine**

7170 The desired compound was prepared according to the method of Example 57, except *t*-Butylcarbazatocarbonylmethyl bromide was used as the alkylating agent. ¹H nmr (300 MHz, DMSO-d₆): δ 9.79 (s, 1 H), 8.85 (s, 1 H), 8.12 (d, 1 H), 7.47-7.29 (m, 6 H), 6.65 (br d, 1 H), 6.56 (d, 1 H), 6.43 (t, 1 H), 4.30 (m, 1 H), 3.81 (d, 2 H), 2.32 (m, 2 H), 2.05 (br s, 6 H), 1.90 (m, 2 H), 1.47 (s, 9 H). MS (APCI +) m/e 517 (M+H)⁺.

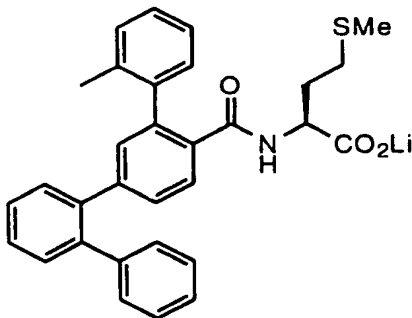


7175

Example 785**N-[4-(2-(thiazol-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 - 211. ¹H nmr (300 MHz, DMSO-d₆): δ 9.01 (s, 1 H), 7.98 (s, 1 H), 7.67 (d, 1 H), 7.63 (m, 1 H), 7.55 (d, 1 H), 7.42 (m, 1 H), 7.30-7.15 (m, 4 H), 3.65 (m, 1 H), 2.18 (m, 2 H), 2.02 (br s, 3 H), 1.92 (br s, 3 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 451 (M-H)⁻.

7180

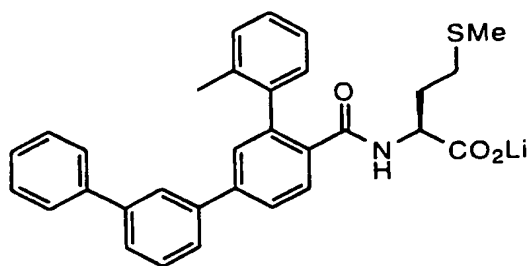


7185

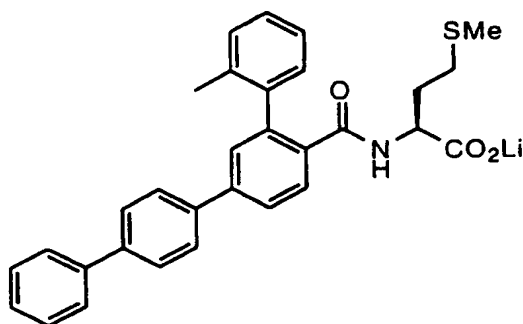
Example 786**N-[4-(2-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 - 211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.96 (s, 1 H), 7.83 (d, 1 H), 7.77 (d, 2 H), 7.74 (d, 1 H), 7.66 (t, 2 H), 7.56 (t, 2 H), 7.48 (t, 2 H), 7.38 (t, 1 H), 7.24 (m, 3 H), 7.02 (m, 1 H), 3.66 (m, 1 H), 2.22 (m, 2 H), 2.05 (br s, 3 H), 1.93 (br s, 3 H), 1.77 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 494 (M-H)⁻.

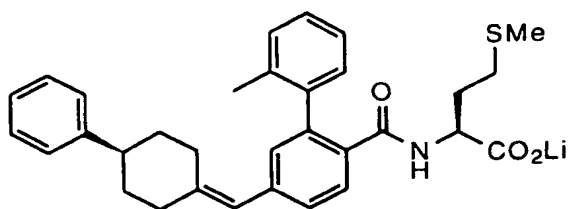
7190

**Example 787****N-[4-(3-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

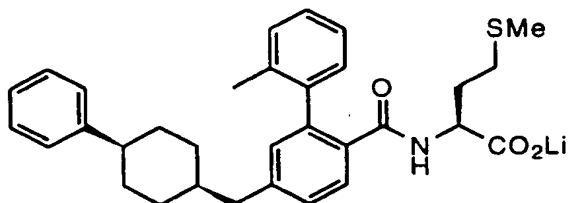
The desired compound was prepared according to the method of Examples 210 - 211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.754-7.44 (m, 4 H), 7.51 (m, 1 H), 7.38 (m, 1 H), 7.34-7.22 (m, 3 H), 7.19-7.00 (m, 5 H), 6.90-6.85 (m, 2 H), 6.66 (m, 1 H), 3.62 (m, 1 H), 2.22 (m, 2 H), 2.05 (br s, 3 H), 1.93 (br s, 3 H), 1.77 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 494 (M-H)⁻.

**Example 788****N-[4-(4-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

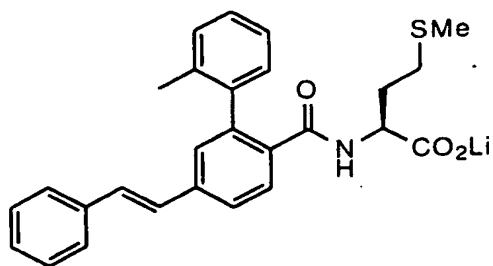
The desired compound was prepared according to the method of Examples 210 - 211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.87-7.80 (m, 3 H), 7.78 (t, 2 H), 7.73 (d, 2 H), 7.65 (d, 1 H), 7.49 (m, 3 H), 7.39 (m, 1 H), 7.33-7.15 (m, 4 H), 7.02 (m, 1 H), 3.66 (m, 1 H), 2.22 (m, 2 H), 2.05 (br s, 3 H), 1.93 (br s, 3 H), 1.77 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 494 (M-H)⁻.

**Example 789****N-[4-(4-phenylcyclohexylidenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

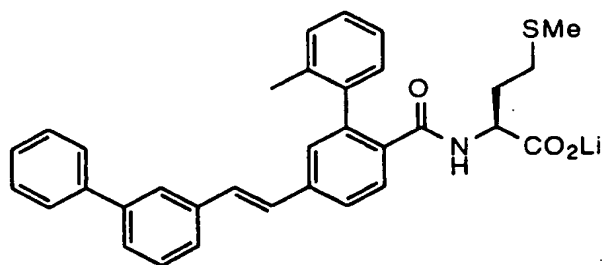
The desired compound was prepared according to the method of Examples 210 - 211. ¹H nmr (300 MHz, CD₃OD): δ 7.56 (m, 1 H), 7.25-6.94 (m, 10 H), 6.27 (s, 1 H), 4.16 (m, 1 H), 2.60 (m, 1 H), 2.40 (m, 2 H), 2.17 (m, 2 H), 2.00-1.70 (m, 13 H), 1.58 (m, 1 H). MS (ESI -): m/e 522 (M-H)⁻.

**Example 790****N-[4-syn-(4-phenylcyclohexylmethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

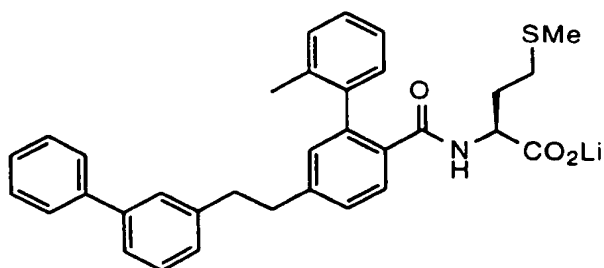
The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, CD₃OD): δ 7.53 (m, 2 H), 7.22-6.92 (m, 10 H), 4.15 (m, 1 H), 2.73 (br d, 2 H), 2.52 (m, 1 H), 2.15 (m, 2 H), 2.02-1.90 (m, 6 H), 1.75 (m, 5 H), 1.57 (m, 5 H). MS (ESI -): m/e 514 (M-H)⁻.

Example 791*N*-[4-(2-phenylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Examples 210 - 211. ¹H nmr (300 MHz, CDCl₃): δ 8.03 (dd, 1 H), 7.61 (dd, 1 H), 7.52 (m, 2 H), 7.40-7.22 (m, 8 H), 7.20 (d, 1 H), 7.10 (d, 1 H), 5.93 (m, 1 H), 4.59 (m, 1 H), 2.20-2.00 (m, 8 H), 1.96 (m, 1 H), 1.56 (m, 1 H). MS (CI +) m/e 446 (M+H)⁺.

Example 792*N*-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211. ¹H nmr (300 MHz, CD₃OD): δ 7.83-7.10 (m, 18 H), 4.27 (m, 1 H), 2.30 (m, 1 H), 2.15-1.95 (m, 8 H), 1.88 (m, 1 H), 1.69 (m, 1 H). MS (ESI -): m/e 520 (M-H)⁻.

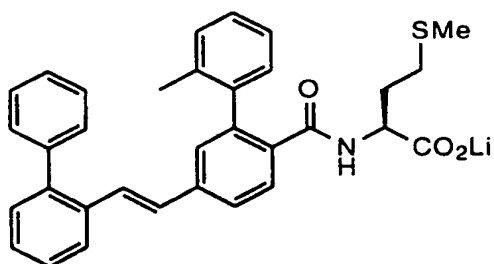


7250

Example 793N-[4-(2-(3-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212.

7255 ^1H nmr (300 MHz, CD_3OD): δ 7.60 (br d, 1 H), 7.51 (br d, 2 H), 7.45-7.20 (m, 12 H), 6.98 (m, 1 H), 4.23 (m, 1 H), 3.04 (br s, 4 H), 2.12 (m, 2 H), 2.03-1.91 (m, 6 H), 1.83 (m, 1 H), 1.65 (m, 1 H). MS (ESI $-$): m/e 522 ($\text{M}-\text{H}$) $^-$.

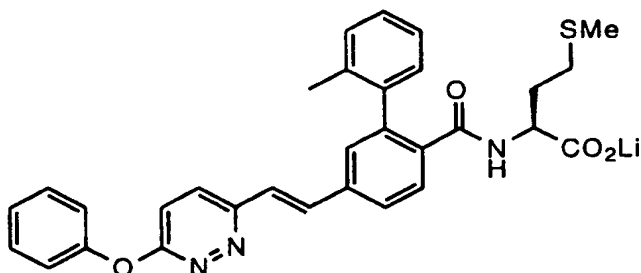


7260

Example 794N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 -

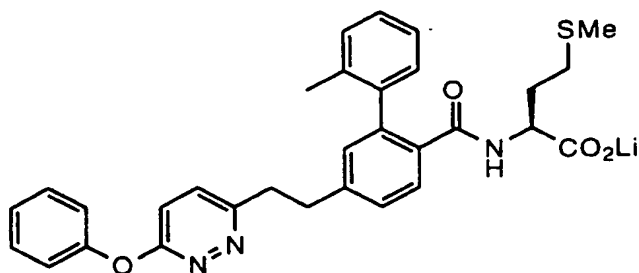
7265 211. ^1H nmr (300 MHz, $\text{DMSO}-d_6$): δ 7.85 (dd, 1 H), 7.54-7.30 (m, 9 H), 7.30-7.10 (m, 6 H), 7.10 (d, 1 H), 6.95 (m, 1 H), 3.67 (m, 1 H), 2.16 (m, 2 H), 2.02 (br s, 3 H), 1.91 (br s, 3 H), 1.70 (m, 1 H), 1.57 (m, 1 H). MS (ESI $-$): m/e 521 ($\text{M}-\text{H}$) $^-$.



Example 810

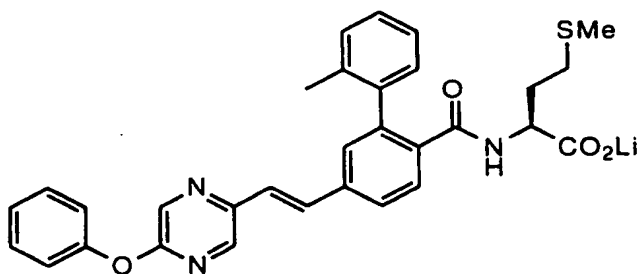
7270 *N*-[4-(2-(3-phenoxy pyridazin-6-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine
 lithium salt

The desired compound was prepared according to the method of Examples 210 -
 211. ¹H nmr (300 MHz, DMSO-d₆): δ 8.08 (d, 1 H), 7.76 (dd, 1 H), 7.59 (d, 1 H), 7.52
 (d, 1 H), 7.52-7.43 (m, 4 H), 7.31-7.10 (m, 7 H), 7.00 (m, 1 H), 2.18 (m, 1 H), 2.02 (m,
 7275 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 538 (M-H)⁻.

Example 811

7280 *N*-[4-(2-(3-phenoxy pyridazin-6-yl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

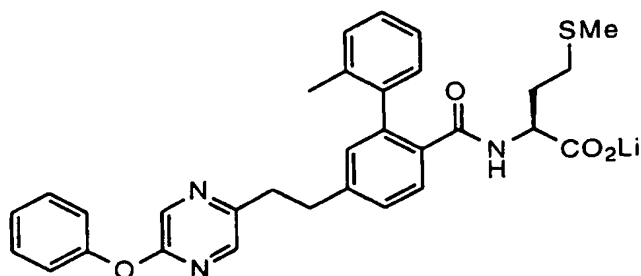
The desired compound was prepared according to the method of Examples 210 -
 211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.65 (d, 1 H), 7.46 (d, 1 H), 7.44 (d, 1 H), 7.38-
 7.10 (m, 9 H), 6.94 (m, 1 H), 6.88 (m, 1 H), 6.75 (m, 1 H), 3.65 (m, 1 H), 3.19 (t, 2 H),
 3.07 (t, 2 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1
 7285 H). MS (ESI -): m/e 540 (M-H)⁻.

Example 812

7290 *N*-[4-(2-(2-phenoxy pyridazin-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine
 lithium salt

The desired compound was prepared according to the method of Examples 210 -
 211. ¹H nmr (300 MHz, DMSO-d₆): δ 8.51 (s, 1 H), 8.33 (s, 1 H), 7.64 (m, 1 H), 7.53-

7295 7.38 (m, 6 H), 7.30-7.15 (m, 7 H), 7.00 (m, 1 H), 3.65 (m, 1 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 538 (M-H)⁻.

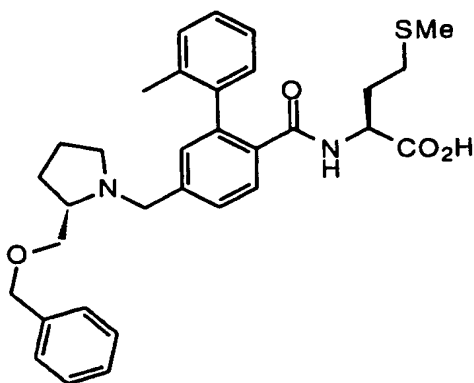


Example 813

7300 N-[4-(2-(2-phenoxy)pyridazin-5-yl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): δ 8.26 (s, 1 H), 8.21 (s, 1 H), 7.50-7.30 (m, 6 H), 7.30-7.10 (m, 5 H), 7.00 (m, 1 H), 3.65 (m, 1 H), 2.97 (m, 4 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 540 (M-H)⁻.

7305

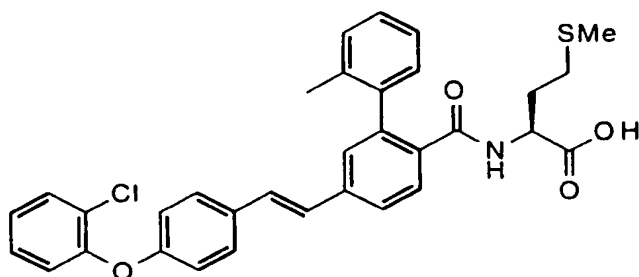


Example 824

7310 N-[4-(2-(benzyloxymethyl)pyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 157. ¹H nmr (300 MHz, DMSO d₆): δ 8.13, d, 1H; 7.47, d, 1H; 7.37, d, 1H; 7.13 - 7.32, m, 10H; 4.48, s, 2H; 4.21, m 2H; 3.51, m, 2H; 3.38, m, 2H; 2.89, m, 2H; 1.99 - 2.40 m, 7H; 1.98, s, 3H; 1.50 - 1.96, m, 4H. MS (ESI(-)): 545 (M-H); (ESI(+)): 547. Calc'd for C₃₂H₃₈N₂O₄S + 0.70 H₂O: C 68.72, H 7.10, N 5.01: Found: C 68.71, H 6.68, N 4.92.

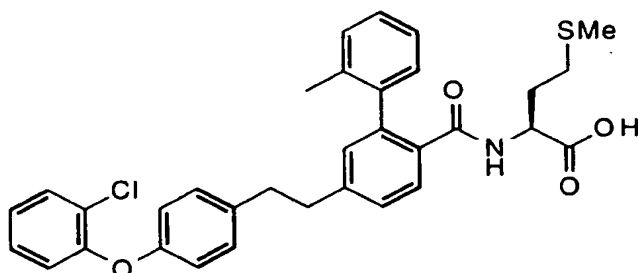
7315

**Example 854**

7320 N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

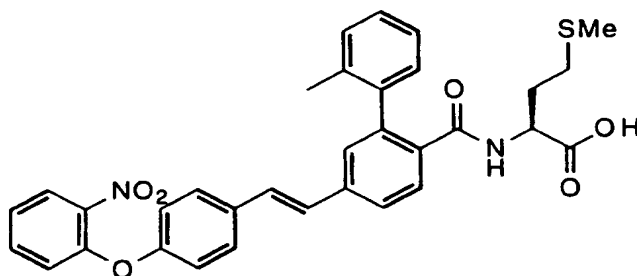
The desired compound was prepared according to the method of Examples 210 -211. MS m/e 570 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.58 (m, 1H), 1.95 (m, 1H), 2.1 (m, 8H), 4.59 (m, 1H), 5.91 (m, 1H), 6.91-7.62 (m, 16H), 8.03 (m, 1H).

7325

**Example 855**

N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine

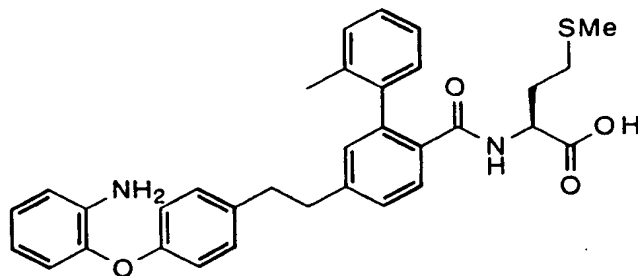
7330 The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 574 (M+H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.53 (m, 1H), 1.93 (m, 1H), 2.1 (m, 8H), 2.95 (m, 4H), 4.59 (m, 1H), 5.83 (m, 1H), 6.83-7.50 (m, 14H), 7.97 (m, 1H).

**Example 856**

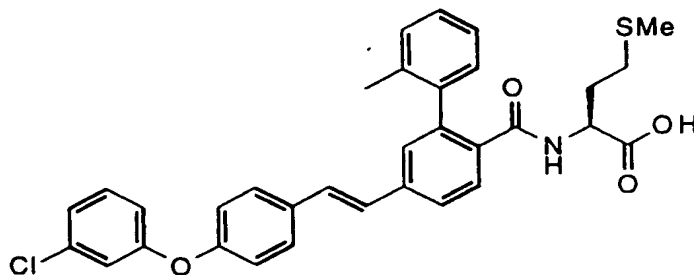
7335

N-[4-(2-(4-(2-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

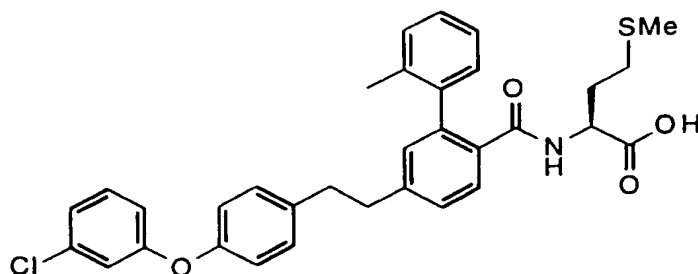
The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 583 (M+H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.57 (m, 1H), 1.93 (m, 1H), 2.1 (m, 8H), 4.58 (m, 1H), 5.90 (m, 1H), 6.65 (m, 2H), 6.90-7.50 (m, 14H), 7.96 (m, 1H).

Example 857N-[4-(2-(4-(2-aminophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine

The title compound was prepared in an analogous manner Example 212 except that the final compound was extracted out of pH 7 buffer after the final hydrolysis. MS m/e 555 (M+H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.49 (m, 1H), 1.91 (m, 1H), 2.1 (m, 8H), 2.95 (m, 4H), 4.56 (m, 1H), 5.84 (m, 1H), 6.68-7.38 (m, 14H), 7.97 (m, 1H).

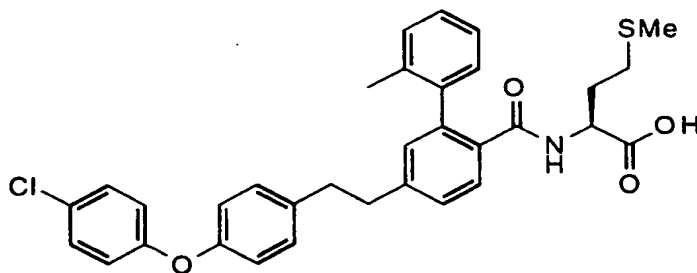
Example 858N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 570 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.57 (m, 1H), 1.95 (m, 1H), 2.1 (m, 8H), 4.59 (m, 1H), 5.91 (m, 1H), 6.91-7.62 (m, 16H), 8.04 (m, 1H).

**Example 859****N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Examples 210 -

7365 212. MS m/e 572 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.49 (m, 1H), 1.93 (m, 1H), 2.1 (m, 8H), 2.97 (m, 4H), 4.55 (m, 1H), 5.84 (m, 1H), 6.81-7.37 (m, 14H), 7.98 (m, 1H).

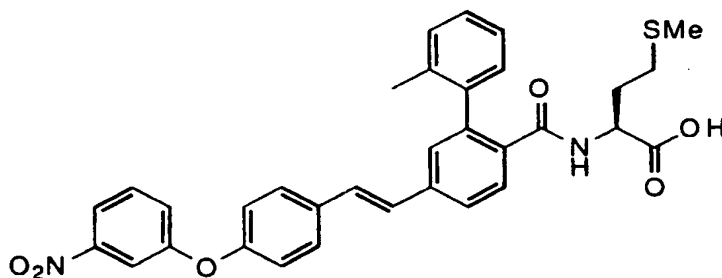


7370

Example 860**N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Examples 210 -

7375 212. MS m/e 574 (M+H)⁺. ¹H NMR (d₆-DMSO, 300 MHz) δ 1.75 (m, 2H), 1.94 (m, 6H), 2.06 (m, 2H), 2.94 (m, 4H), 4.13 (m, 1H), 6.92-7.48 (m, 12H), 7.66 (m, 2H), 7.97 (m, 1H).



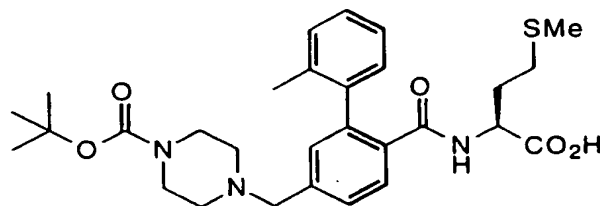
7380

Example 861

N-[4-(2-(4-(3-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 583 (M+H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.54 (m, 1H), 1.92 (m, 1H), 2.1 (m, 8H), 4.58 (m, 1H), 5.91 (m, 1H), 6.7-7.6 (m, 16H), 8.02 (m, 1H).

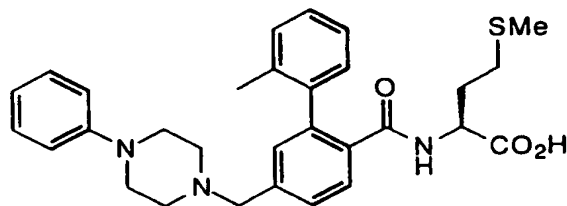
7385

Example 866N-[4-(4-t-butoxycarbonylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. ¹H NMR (CDCl₃, 300 MHz) δ 1.45 (s, 9H), 1.60 (m, 1H), 1.82 (m, 1H), 2.05 (m, 8H), 2.53 (m, 4H), 3.46 (m, 4H), 3.62 (m, 2H), 4.38 (m, 1H), 6.00 (m, 1H), 7.10-7.50 (m, 6H), 7.86 (m, 1H). MS m/e 540 (M-H)⁻.

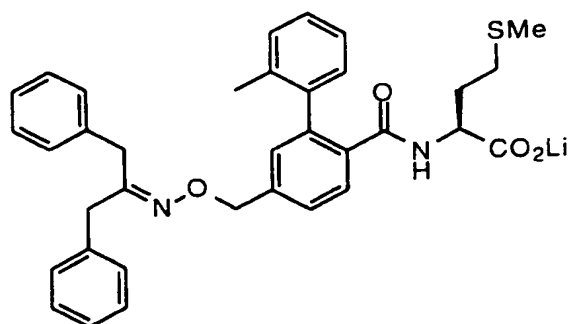
7390

7395

Example 867N-[4-(4-phenylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. ¹H NMR (CDCl₃, 300 MHz) δ 1.47 (m, 1H), 1.82 (m, 1H), 2.0 (m, 8H), 2.75 (m, 4H), 3.21 (m, 4H), 3.65 (m, 2H), 4.30 (m, 1H), 6.11 (m, 1H), 6.89 (m, 2H), 7.22 (m, 8H), 7.40 (m, 1H), 7.82 (m, 1H). MS m/e 516 (M-H)⁻.

7400

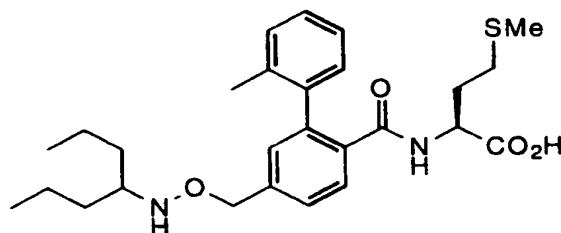


7405

Example 888**N-[4-N-(1,3-Diphenylpropan-2-yl)iminooxymethyl]-2-(2-methylphenyl)benzoyl-methionine lithium salt**

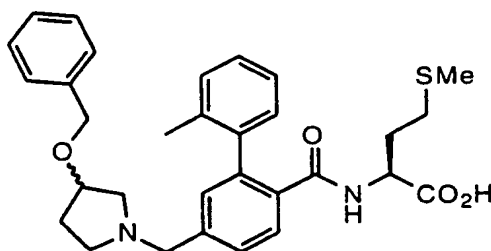
The desired compound was prepared according to the method of Example 157. ¹H NMR (300 MHz, DMSO) δ 1.50-1.62 (m, 1H), 1.63-1.76 (m, 1H), 1.92 (s, 3H), 1.95-2.15 (m, 5H), 3.38 (s, 2H), 3.53 (s, 2H), 3.69 (brs, 1H), 5.18 (s, 2H), 6.98 (d, J=6.4 Hz, 1H), 7.04-7.28 (m, 15H), 7.36 (dd, J=7.8, 1.7 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H). MS (ESI) m/z 587 (M+H); Analysis calc'd for C₃₅H₃₅LiN₂O₄S•1.0H₂O: C, 69.52; H, 6.17; N, 4.63; found: C, 69.47; H, 6.09; N, 4.58.

7415

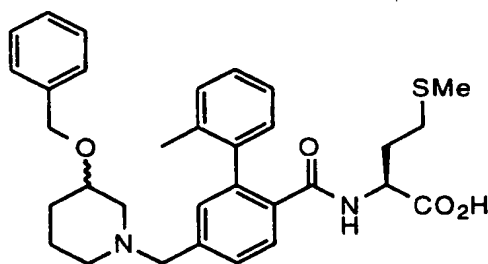
**Example 929****N-[4-(N-Hept-4-ylaminooxymethyl)-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Example 157. ¹H (300MHz, DMSO-d₆, δ) 7.52 (1H, d, J=8Hz), 7.37 (1H, dd, J=9&2Hz), 7.30-7.10 (4H, m), 7.10 (1H, bs), 6.97 (1H, m), 6.33 (1H, bd, J=10Hz), 4.63 (2H, s), 3.68 (1H, m), 2.74 (1H, m), 2.20-1.95 (3H, m), 1.92 (3H, s), 1.90-1.40 (4H, m), 1.40-1.20 (8H, m), 0.83 (6H, t, J=8Hz). m/z (ESI) 485 (MH⁺) Anal.calc. for C₂₇H₃₇LiN₂O₄S•0.25 H₂O C 65.24, H 7.60, N 5.64 Found C 65.14, H 7.81, N 5.33

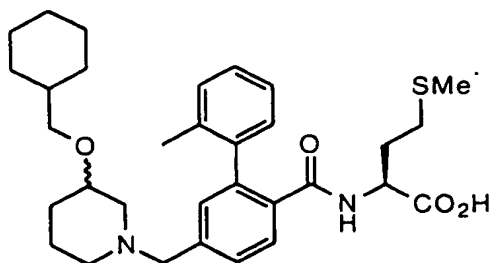
7425

**Example 988****N-[4-(3-benzyloxypyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoylmethionine**

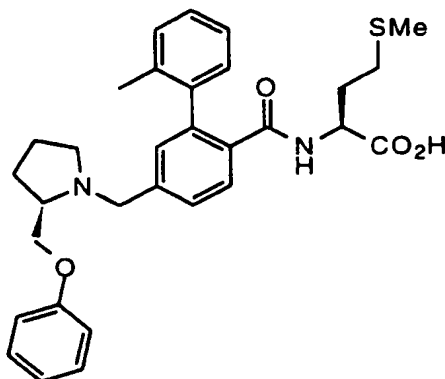
The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 8.08, d, 1H; 7.47, d, 1H; 7.37, dd, 1H; 7.29, m, 5H; 7.20, m, 2H; 7.14, m, 3H; 4.40, q (AA'), 2H; 4.21, m, 1H; 4.11, m, 1H; 3.68, q (AA'), 2H; 2.41 - 2.76, m, 4H; 1.98 - 2.23, m, 6H; 1.97, s, 3H; 1.64 - 1.93, m, 3H. MS (ESI(-)): 531 (M-H); (ESI(+)): 533. Calc'd for C₃₁H₃₆N₂O₄S: C 69.90, H 6.81, N 5.26: Found: C 69.21, H 6.86, N 5.06

**Example 989****N-[4-(3-benzyloxypiperidin-1-yl)methyl]-2-(2-methylphenyl)benzoylmethionine**

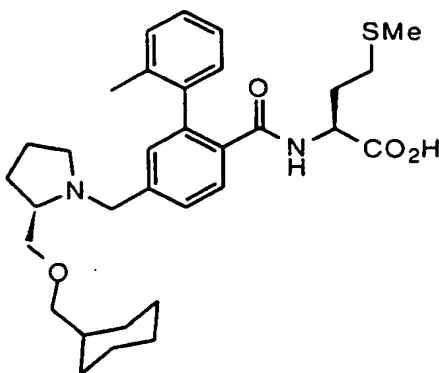
The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 8.09, d, 1H; 7.49, d, 1H; 7.37, dd, 1H; 7.23 - 7.34, m, 5H; 7.22, m, 2H; 7.12, m, 3H; 4.48, s, 2H; 4.23, ddd, 1H; 3.60, m, 2H; 3.46, m, 1H; 3.30, m, 2H; 2.95, m, 1H; 2.64, m, 1H; 2.00 - 2.24, m, 6H; 1.98, s, 3H; 1.63 - 1.96, m, 3H; 1.42, m, 1H; 1.22, m, 1H. MS (ESI(-)): 545 (M-H); (ESI(+)): 547. Calc'd for C₃₂H₃₈N₂O₄S + 0.37 H₂O: C 69.46, H 7.06, N 5.06: Found: C 69.45, H 7.14, N 4.76.

**Example 990****N-[4-(3-cyclohexylmethoxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 7.98, d, 0.5H; 7.97, d, 0.5H; 7.37, d, 1H; 7.25, d, 1H; 7.09, m, 2H; 7.02, m, 3H; 4.10, m, 1H; 3.44, s, 2H; 3.15, m, 2H; 3.05, m, 2H; 2.77, m, 1H; 2.52, m, 1H; 1.88 - 2.13, m, 5H; 1.60 - 1.82, m, 3H; 1.51, m, 5H; 1.85, s, 3H; 1.30, m, 2H; 0.90 - 1.16, m, 4H; 0.75, m, 2H. MS (ESI(-)): 551 (M-H); (ESI(+)): 553. Calc'd for C₃₂H₄₄N₂O₄S + 1.13 H₂O: C 67.06, H 8.14, N 4.89: Found: C 67.06, H 7.88, N 4.80.

**Example 991****N-[4-(2-phenoxyethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 8.10, d, 1H; 7.48, d, 1H; 7.40, d, 1H; 7.01 - 7.30, m, 6H; 6.90, m, 3H; 4.22, m, 2H; 4.01, m, 1H; 3.85, m, 1H; 3.59, m, 1H; 3.34, m, 1H; 3.03, m, 1H; 2.91, m, 1H; 2.36, m, 1H; 1.98 - 2.24, m, 6H; 1.96, s, 3H; 1.60 - 1.90, m, 4H. MS (ESI(-)): 531 (M-H); (ESI(+)): 533. Calc'd for C₃₁H₃₆N₂O₄S + 0.87 H₂O: C 67.90, H 6.94, N 5.11: Found: C 67.90, H 6.95, N 4.87.

Example 992

7475

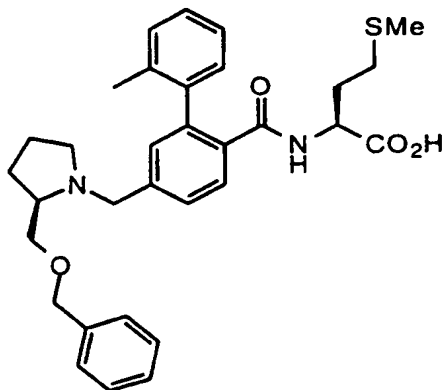
N-[4-(2-cyclohexylmethoxymethyl)pyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoylmethionine

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 8.11, d, 1H; 7.47, d, 1H; 7.38, d, 1H; 7.21, m, 2H;

7480

7.16, m, 3H; 4.21, m, 2H; 3.53, m, 1H; 3.25 - 3.46, m, 3H; 3.18, dq (AA'), 2H; 2.87, m, 2H; 2.30, m, 1H; 1.99 - 2.24, m, 6H; 1.97, s, 3H; 1.77 - 1.95, m, 2H; 1.56 - 1.76, m, 6H; 1.40 - 1.55, m, 2H; 1.51, m, 3H; 0.88, m, 2H. MS (ESI(-)): 551 (M-H); (ESI(+)): 553. Calc'd for C₃₂H₄₄N₂O₄S + 0.74 H₂O: C 67.90, H 8.10, N 4.95: Found: C 67.89, H 7.83, N 4.79.

7485

Example 993

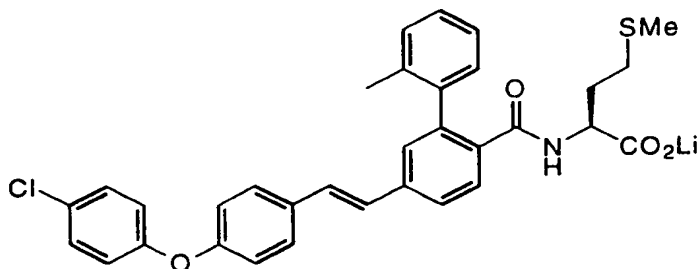
N-[4-(2-benzyloxymethyl)pyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoylmethionine

7490

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 8.12, d, 1H; 7.49, d, 1H; 7.39, d, 1H; 7.30, m, 5H; 7.21, m, 2H; 7.15, m, 3H; 4.48, s, 2H; 4.22, m, 2H; 3.53, m, 2H; 3.40, m, 2H; 2.89, m, 2H; 2.23 - 2.40, m, 1H; 2.00 - 2.22, m, 5H; 1.98, s, 3H; 1.50 - 1.94, m, 6H. MS (ESI(-)):

545 (M-H); (ESI(+)): 547. Calc'd for $C_{32}H_{38}N_2O_4S + 1.60 H_2O$: C 66.78, H 7.22, N 4.87; Found: C 66.79, H 6.88, N 4.70.

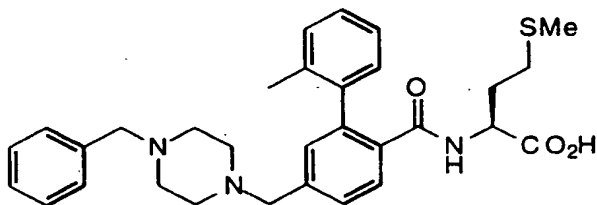
7495

Example 1016

7500 N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

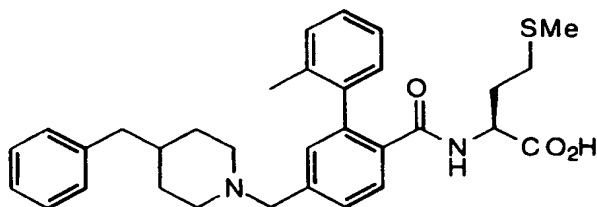
Prepared as in Example 210. MS m/e 570 (M-H)⁻. ¹H NMR (d₆-DMSO, 300 MHz) δ 1.5-2.2 (m, 10H), 3.65 (m, 1H), 6.95 (m, 1H), 7.02-7.69 (m, 17H).

7505

Example 1035

N-[4-(4-benzylpiperazin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

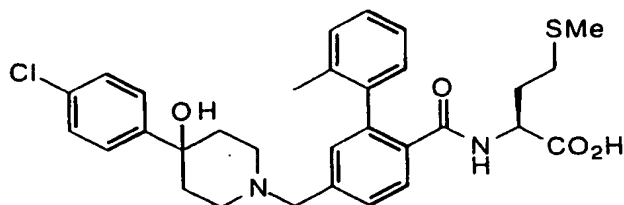
7510 Prepared similarly. MS m/e 530 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.65 (m, 1H), 1.95 (m, 1H), 2.08 (m, 8H), 2.75 (m, 8H), 3.71 (m, 4H), 4.42 (m, 1H), 6.21 (m, 1H), 7.3 (m, 11H), 7.79 (m, 1H).

Example 1036

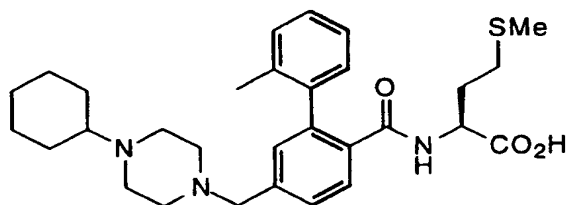
7515

N-[4-(4-benzylpiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

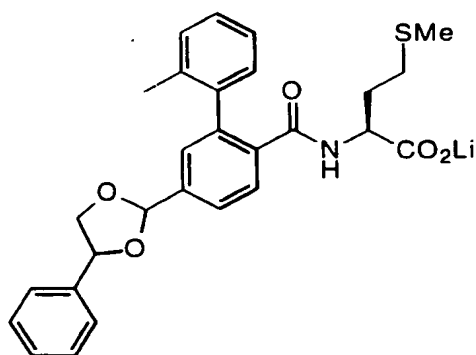
Prepared similarly. MS m/e 529 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.65 (m, 5H), 1.95 (m, 1H), 2.06 (m, 8H), 2.41 (m, 1H), 2.56 (m, 2H), 3.30 (m, 2H), 3.55 (m, 1H), 3.71 (m, 2H), 4.13 (m, 1H), 4.42 (m, 1H), 6.30 (m, 1H), 7.18 (m, 10H), 7.47 (m, 1H), 7.77 (m, 1H).

Example 1037N-[4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

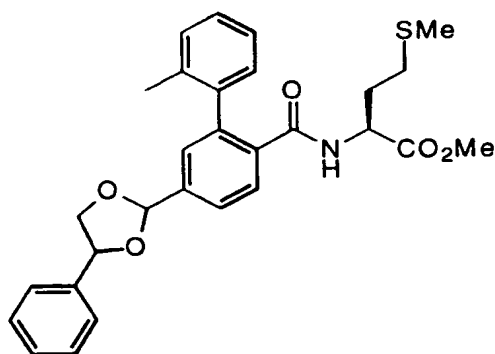
Prepared similarly. MS m/e 565 (M-H)⁻. ¹H NMR (d₆-DMSO, 300 MHz) δ 1.61 (m, 4H), 1.80 (m, 1H), 1.93 (m, 1H), 1.99 (s, 3H), 2.15 (m, 5H), 2.48 (m, 2H), 2.69 (m, 2H), 3.63 (s, 2H), 4.18 (m, 1H), 4.92 (s, 1H), 6.95 (m, 2H), 7.45 (m, 8H), 7.95 (m, 1H).

Example 1038N-[4-(4-cyclohexylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Prepared similarly. MS m/e 522 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.29 (m, 6H), 1.68 (m, 1H), 1.88 (m, 5H), 2.05 (m, 8H), 2.71 (m, 4H), 2.89 (m, 1H), 3.58 (m, 6H), 4.38 (m, 1H), 6.42 (m, 1H), 7.2-7.5 (m, 6H), 7.74 (m, 1H).

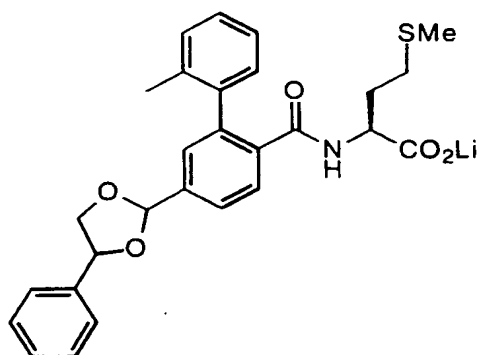
Example 1083

(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine, Lithium Salt

Example 1083A

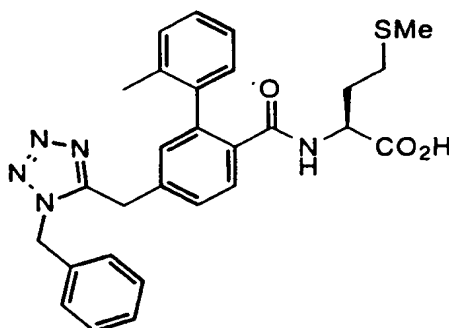
(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

To a solution of N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester (example 403G, 340mg) and 1,2-dihydroxyethylbenzene (134mg) in toluene (3mL) was added *p*-toluenesulfonic acid hydrate (17mg), and magnesium sulfate (212mg). After 7h at ambient temperature, the reaction was filtered through infusorial earth and concentrated. The residue was purified by silica gel chromatography eluting with 30% EtOAc/hexane to give the title compound as a colorless oil (330mg, 74%). MS (APCI(+)) *m/e* 506 (M+H)⁺. MS (APCI(-)) *m/e* 540 (M+Cl)⁻.

**Example 1083B**

(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine. Lithium Salt

7560 The title compound was prepared from (2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine methyl ester according to the procedure in example 608E, and was isolated as a white powder. ¹H NMR (300 MHz, DMSO) δ 1.51-1.88 (m, 4H), 1.92 (s, 3H), 1.98-2.20 (m, 3H), 3.62-3.73 (m, 1H), 3.76 (t, J=7.8 Hz, 0.5H), 3.85 (t, J=7.2 Hz, 0.5H), 4.38 (t, J=7.2 Hz, 0.5H), 4.56 (ddd, J=8.4, 6.6, 1.8 Hz, 0.5H), 5.25 (t, J=6.9 Hz, 1H), 6.20 (s, 0.5H), 6.22 (s, 0.5H), 7.00-7.12 (m, 1H), 7.25-7.47 (m, 10H), 7.59 (d, J=6 Hz, 2H). MS (APCI(+)) m/e 492 (M+H); Analysis calc'd for C₂₈H₂₈LiNO₅S•1.30H₂O: C, 64.56; H, 5.92; N, 2.69; found: C, 64.56; H, 5.69; N, 2.54



7570

Example 1099

N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7575

Step 1: 4-nitrilemethyl-2-(2-methylphenyl)phenylacetate

A 100 mL round-bottom flask was charged with 4-bromomethyl-2-(2-methylphenyl)phenylacetate (798.0 mg, 2.5 mmol) and MeOH (23 mL)/ H₂O (2 mL). Potassium cyanide (489.4 mg, 7.5 mmol) was added and allowed to stir at room

temperature for 12 h, then heated to reflux for 1 h, monitoring by TLC (1:1 EtOAc/hexane).
7580 The reaction was cooled and solvent was removed under vacuum. It was then diluted with
water and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed
with brine, dried over MgSO₄, filtered and concentrated under vacuum. The product was
purified by silica gel column (1:1 EtOAc/Hexane). Yield: 597.3 mg (90%), off-white solid.
¹H NMR (δ, CDCl₃): 8.0 (2H), 7.0-7.5 (5H), 2.83 (2H), 3.6 (3H), 2.05 (3H), 1.55 (1H).
7585 Mass spec(ESI): 266 (M+1), 264 (M-1).

Step 2: 4-tetrazol-5-ylmethyl-2-(2-methylphenyl)phenylacetate

A 100 mL 3-neck round-bottom flask was charged with 4-nitrilemethyl-2-(2-
methylphenyl)phenylacetate (533.3 mg, 2 mmol) and dmf (25 mL) under N₂ purge.
7590 Sodium azide (910.1 mg, 12 mmol) and triethylamine hydrochloride (1.3780 g, 10 mmol)
were added. The reaction was heated at 100 °C for 48 h. After cooling, 1 M NaHCO₃ (50
mL) was added. The reaction was extracted with Et₂O (3 x 25 mL). The aqueous layer was
acidified with 1 M H₃PO₄ to pH = 3. Then extracted with EtOAc (3 x 50 mL). The
combined organic layers were washed with water (50 mL) and brine (50 mL), dried over
7595 MgSO₄, filtered and concentrated under vacuum. The product was purified by silica gel
column (CHCl₃/MeOH/HOAc (95:5:1)). Yield: 691.2 mg, yellow oil. Mass spec(ESI): 309
(M+1), 307 (M-1).

Step 3: 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoate (A) and 4-(2-
benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoate (B)

A 25 mL round-bottom flask was charged with 4-tetrazol-5-ylmethyl-2-(2-
methylphenyl)phenylacetate (618.1 mg, 2 mmol) in CH₃CN (9.5 mL)/water (0.5 mL).
Benzyl bromide (0.36 mL, 3 mmol) and potassium hydrogen carbonate (1 g) were added.
The reaction was stirred for 4 h and then diluted with water. The mixture was extracted
7605 with Et₂O (3 x 10 mL). The organic layer was washed with water (10 mL) and brine (10
mL), dried over MgSO₄, filtered and concentrated under vacuum. The two regioisomers
were separated by silica gel column (40% EtOAc/Hexane). Yield: 255.7 mg (product A)
and 277.6 mg (product B). Product A: ¹H NMR (δ, CDCl₃): 7.9 (2H), 7.0-7.4 (10H),
5.7 (2H), 4.27 (2H), 3.6 (3H), 2.0 (3H). Mass spec(ESI): 399 (M+1), 397 (M-1).
7610 Product B: ¹H NMR (δ, CDCl₃): 7.9 (2H), 6.9-7.4 (10H), 5.4 (2H), 4.2 (2H), 3.6 (3H),
2.0 (3H). Mass spec(ESI): 399 (M+1), 397 (M-1).

Step 4: 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoic acid

A 50 mL round-bottom flask was charged with 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoate (A) (205.8 mg, 0.52 mmol) and ethanol (10 mL). 4 N sodium hydroxide (1.1 mL, 4.16 mmol) was added. The reaction was refluxed for 2 h and then cooled. The solvent was removed under vacuum and then diluted with water. The reaction was extracted with Et₂O (3 x 10 mL). The pH of the aqueous layer was adjusted to 2 with 1 M H₃PO₄. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under vacuum. Yield: 205.1 mg, white solid. ¹H NMR (δ, CDCl₃): 8.0 (2H), 7.0-7.4 (10H), 5.7 (2H), 4.3 (2H), 2.0 (3H).

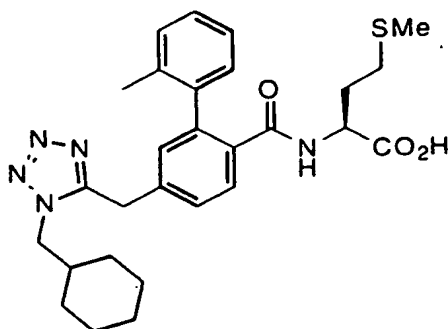
Step 5: N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

A 50 mL round-bottom flask was charged with 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoic acid (205.1 mg, 0.52 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) (110.1 mg, 0.572 mmol), L-methionine methyl ester hydrochloride (135.0 mg, 0.676 mmol), 1-hydroxybenzotriazole (78.6 mg, 0.572 mmol) and dmf (3 mL). The reagents were stirred until completely dissolved and then triethylamine (0.14 mL, 0.936 mmol) was added. The reaction was stirred about 48 h until no starting material was present. Water (2 mL) and EtOAc (2 mL) were added to dissolve the precipitate. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with 2 M Na₂CO₃ (10 mL), water (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated under vacuum. Yield: 273.0 mg, yellow solid. ¹H NMR (δ, CDCl₃): 8.0 (2H), 7.0-7.4 (10H), 5.85 (1H), 5.7 (2H), 4.6 (1H), 4.3 (2H), 3.65 (3H), 1.95-2.2 (6H), 1.5-1.9 (4H).

Step 6: N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine-carboxylic acid

A 25 mL round-bottom flask was charged with N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine (273.0 mg, 0.53 mmol) and 3 mL of MeOH/THF (1:1). The flask was cooled to 0°C and 1 M lithium hydroxide (1.1 mL, 1.07 mmol) was added. The bath was removed and the reaction stirred for about 3 h, monitoring by TLC (1:1 EtOAc/Hexane). The solvent was removed under vacuum and the reaction diluted with water. The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under vacuum. Yield: 176.2 mg yellow solid. ¹H NMR (δ, CDCl₃): 7.9 (2H), 7.0-7.4 (10H), 5.9 (1H), 5.7 (2H), 4.57 (1H), 4.3 (2H), 2.0-2.2 (6H), 1.9 (2H), 1.5 (2H).

7650 Mass spec (ESI): 516 (M+1), 514 (M-1) $C_{28}H_{29}N_5O_3S \cdot 1.30 H_2O$
 Anal. Calc'd.: C 62.39 H 5.91 N 12.99. Found: C 62.43 H 5.64 N 12.83



7655 Example 1100

N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

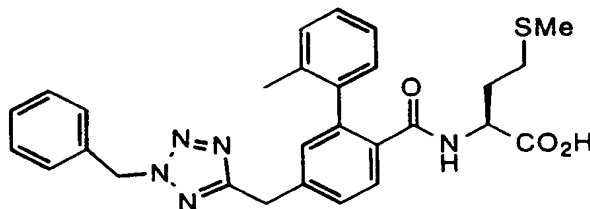
Procedure: Follow example 1102 (product B). Yield: 105.7 mg, pale yellow solid.

N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine.

1H NMR (δ , $CDCl_3$): 7.95 (1H), 7.0-7.4 (5H), 5.9 (1H), 4.55 (1H), 4.3 (2H), 4.0 (2H),
 2.9 (3H), 0.8-2.2 (20H)

7660 Mass spec (ESI): 522 (M+1), 520 (M-1) $C_{28}H_{35}N_5O_3S \cdot 0.90 H_2O \cdot 0.05 CH_3CN$

Anal Calc'd.: C 62.51 H 6.90 N 13.10 Found: C 62.51 H 6.43 N 12.92



7665 Example 1101

N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Procedure: Follow example 1099 (product B). Yield: 176.2 mg.

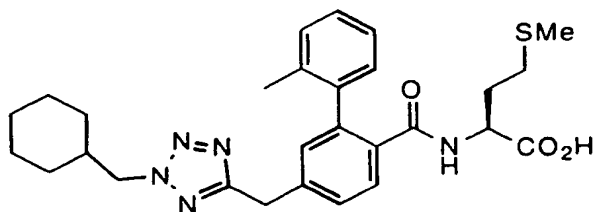
7670 N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine.

1H NMR (δ , $CDCl_3$): 7.92 (2H), 6.8-7.4 (10H), 5.9 (1H), 5.4 (2H), 4.55 (1H), 4.2 (2H),
 2.0-2.2 (6H), 1.9 (2H), 1.55 (2H)

Mass spec (ESI): 516 (M+1), 514 (M-1) $C_{28}H_{29}N_5O_3S \cdot 1.30 H_2O$

Anal. calc'd.: C 62.39 H 5.91 N 12.99 Found: C 62.43 H 5.65 N 12.53

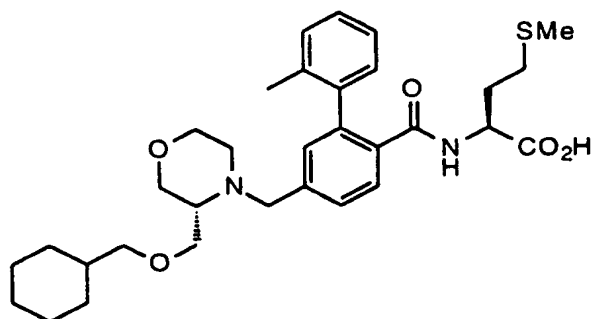
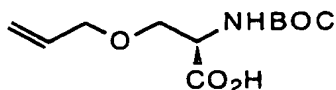
7675

**Example 1102****N-[4-(2-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine**

7680 Procedure: Follow example 1099, except use bromomethylcyclohexane instead of benzylbromide (product A). Yield: 220.2 mg, pale yellow solid. N-[4-(2-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine
¹H NMR (δ, CDCl₃): 7.95 (1H), 7.0-7.5 (5H), 5.9 (1H), 4.55 (1H), 4.4 (2H), 4.3 (2H), 2.9 (3H), 0.9-2.2 (20H)

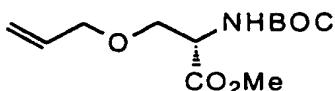
7685 Mass spec (ESI): 522 (M+1), 520 (M-1) C₂₈H₃₅N₅O₃S•0.50H₂O

Anal. Calc'd.: C 63.37 H 6.84 N 13.20 Found: C 63.58 H 6.54 N 12.80

**Example 1109****N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine****Example 1109A****O-Allyl-N-t-butoxycarbonyl-L-serine**

7695 Serine (5.13 g, 25.0 mmol) in 60 mL of DMF was cooled in an ice bath and treated with sodium hydride (60%, 3.30 g, 82.5 mmol) in 3 portions over ~ 15 minutes and the mixture stirred until the cessation of bubbling (~20 minutes). The mixture was treated with
 7700 allyl bromide (2.4 mL, 27.5 mmol) and after 5 minutes, the ice bath was removed. The

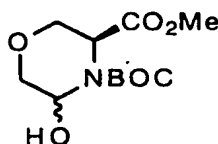
mixture was stirred for 1.5 hours at ambient temperature and then quenched by the careful addition of water. The pH of the solution was adjusted to 2 with 1M aqueous phosphoric acid and extracted with 3 portions of ethyl acetate. The combined organic fractions were extracted with 3-30 mL portions of 1N aqueous sodium hydroxide and the combined aqueous phases washed with ether. The pH of the aqueous phase was adjusted to 2 with 1M aqueous phosphoric acid and extracted with 3 portions of ethyl acetate. The combined organic fractions were washed with water and brine, dried, filtered and concentrated to provide 6.10 g (99%) of the title compound. MS (DCI, NH₃): 246 (MH⁺); 263 (M+NH₄)⁺.



Example 1109B

O-Allyl-N-t-butoxycarbonyl-L-serine, methyl ester

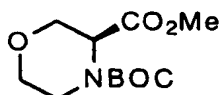
A solution of example 1109A (6.09 g, 24.8 mmol) in 30 mL of 50% aqueous DMF was treated with cesium carbonate (8.09, 24.8 mmol) and the mixture stirred 30 minutes. Methyl iodide (3.1 mL, 49.7 mmol) was added and the mixture stirred for 60 hours at ambient temperature. The mixture was diluted with water and extracted with 3 portions of ethyl ether. The combined organic extracts were washed with water, 1N aqueous sodium hydroxide and brine, dried filtered and concentrated to provide 1.51 g (23%) of the title compound. MS (DCI, NH₃): 260 (MH⁺); 277 (M+NH₄)⁺.



Example 1109C

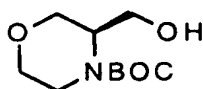
3(S)-Methoxycarbonyl-4-t-butoxycarbonyl-5-hydroxymorpholine

Ozone was passed through a solution of example 1109B (1.50 g, 5.8 mmol) in 20 mL of 1:1 methanol/methylene chloride cooled in a dry ice/acetone bath until the solution turned blue. Nitrogen was passed through the cold solution until the blue color was discharged and then dimethyl sulfide (3 mL) was added and the cooling bath removed and the mixture stirred overnight and concentrated. The residue was dissolved in ether and washed with water, brine, dried, filtered and concentrated to provide 1.5 g of the title compound that was used directly.

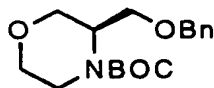


Example 1109D3(S)-Methoxycarbonyl-4-t-butoxycarbonylmorpholine

7735 A solution of example 1109C (522 mg, 2.0 mmol) in 4 mL of methylene chloride was cooled in an ice/acetone bath and triethylsilane (1.6 mL, 10.0 mmol) was added. The solution was then treated with a solution of boron trifluoride etherate (0.27 mL, 2.2 mmol) in 1 mL of methylene chloride. After stirring 30 minutes, the bath was removed and stirring continued for 30 minutes and the mixture was quenched by the addition of 2M aqueous sodium carbonate. The mixture was diluted with water and methylene chloride and the layers separated. The aqueous layer was extracted with 2 portions of methylene chloride and the combined organic layers were dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (40 g, 20% ethyl acetate/hexanes) to provide 200 mg (41%) of the title compound. MS (DCI, NH₃): 246 (MH⁺); 263 (M+NH₄)⁺.

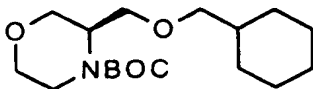
Example 1109E3(S)-Hydroxymethyl-4-t-butoxycarbonylmorpholine

7750 A solution of example 1109D (376 mg, 1.53 mmol) in 4 mL of ethanol was treated with calcium chloride (310 mg, 3.06 mmol) and the mixture stirred until a clear solution resulted. The solution was diluted with 2 mL of THF and then treated with sodium borohydride (232 mg, 6.13 mmol) and the mixture stirred for 4 hours. The reaction was quenched by the addition of water, diluted with 2M aqueous sodium carbonate and extracted with 3 portions of methylene chloride. The combined organic fractions were dried, filtered and concentrated to provide 268 mg (83%) of the title compound. MS (DCI, NH₃): 218 (MH⁺); 235 (M+NH₄)⁺.

Example 1109F3(S)-Benzyloxymethyl-4-t-butoxycarbonylmorpholine

7760 A solution of example 1109E (261 mg, 1.2 mmol) and benzyl bromide (0.18 mL, 1.44 mmol) in 1 mL of DMF was cooled in an ice bath and treated with sodium hydride (60%, 72 mg, 1.80 mmol) and the mixture stirred for 15 minutes. The cooling bath was removed and stirring continued for 6 hours and then the mixture was quenched by the addition of water. The mixture was partitioned between water and 3 portions of ethyl

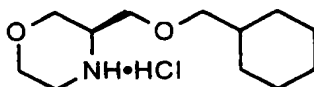
acetate. The combined organic extracts were washed with water, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (20 g, 25% ethyl acetate/hexanes) to provide 275 mg (74%) of the title compound. MS (DCI, NH₃): 308 (MH⁺); 325 (M+NH₄)⁺.



Example 1109G

3(S)-Cyclohexylmethyloxymethyl-4-t-butoxycarbonylmorpholine

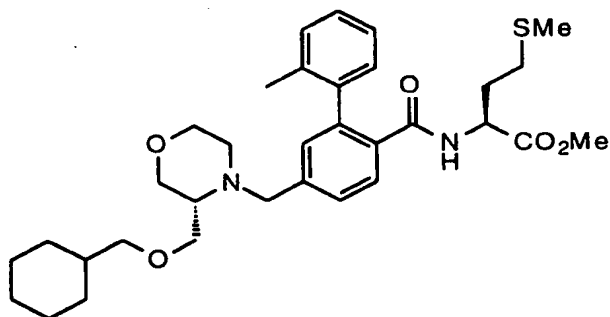
A solution of example 1109F (270 mg, 0.88 mmol) in 15 mL of methanol was treated with 135 mg of 5% rhodium on alumina and stirred under 4 atmospheres of hydrogen gas for 24 hours. The mixture was filtered and concentrated to provide 274 mg (99%) of the title compound. MS (DCI, NH₃): 314 (MH⁺).



Example 1109H

3(S)-Cyclohexylmethyloxymethylmorpholine

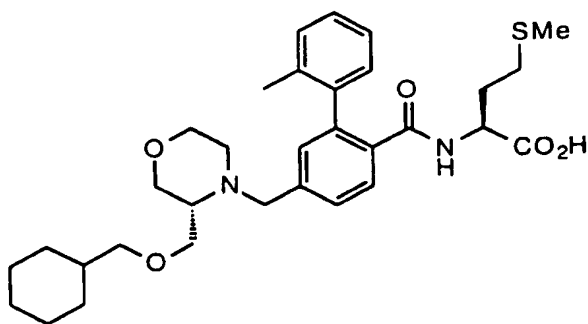
Using the procedure of example 1106C, example 1109G (265 mg, 0.84 mmol) was converted to the title compound. MS (DCI, NH₃): 214 (MH⁺).



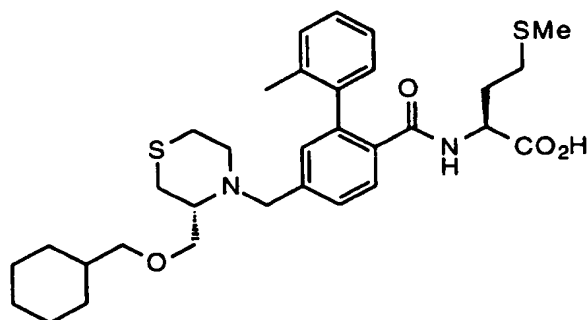
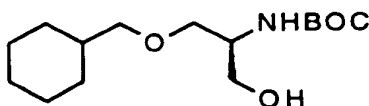
Example 1109I

N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

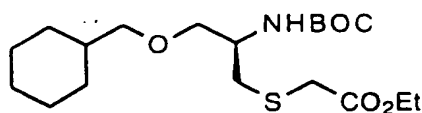
Using the procedure described in example 1106C, part 1, example 1109H (204 mg, 0.82 mmol) provided 29 mg (10%) of the title compound. MS (ESI⁺): 583 (MH⁺); (ESI⁻): 581 (M-H).

**Example 1109J****N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine**

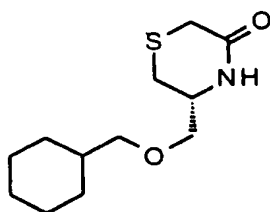
Prepared according to the procedure of example 1104D. ¹H nmr (300 MHz., CD₃OD): δ 7.64, d, 1H; 7.48, d, 1H; 7.14 - 7.34, m, 5H; 4.41, m, 1H; 4.28, bd, 1H; 3.85, dd, 1H; 3.76, m, 1H; 3.49, 3.70, m, 6H; 3.23, d, 2H; 2.82, m, 2H; 2.51, m, 1H; 2.06 - 2.24, m, 5H; 1.99, s, 3H; 1.93, m, 2H; 1.70, m, 6H; 1.55, m, 1H; 1.09 - 1.32, m, 4H; 0.92, m, 2H. MS (ESI+): 569 (MH⁺); (ESI-): 567 (M-H). Calc'd for C₃₂H₄₄N₂O₅S•0.40 H₂O; C 66.73; H 7.84; N 4.86; Found: C 66.72; H 7.82; N 4.71.

**Example 1111F****N-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine****Example 1111A****3(S)-cyclohexylmethoxy-2-t-butoxycarbonylaminopropan-1-ol**

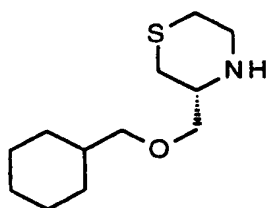
Following the procedure of example 1109G, example 1108A (1.00g, 3.55 mmol) was converted to 0.85 g (83%) of the title compound. MS (DCI, NH₃): 288 (MH⁺).

Example 1111BR-[2-t-butoxycarbonylamino-3-cyclohexylmethyloxy]propylmercaptoacetic acid, ethyl ester

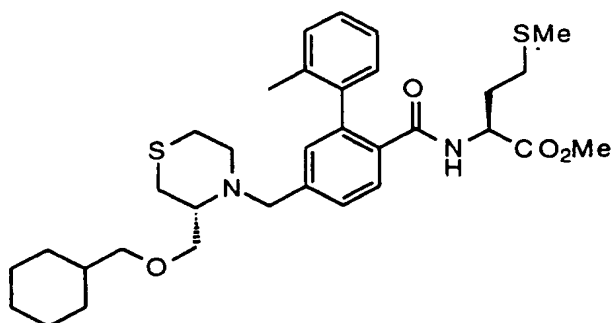
7820 Following the procedure described in example 1106B (and substituting the potassium salt of ethyl mercaptoacetate for sodium thiomethoxide), example 1111A (0.84 g, 2.91 mmol) was converted to 0.89 g (78% overall) the title compound. MS (DCI, NH₃): 390 (MH⁺).

Example 1111C3-Oxo-5(R)-cyclohexylmethyloxymethyl-thiomorpholine

7830 Example 1111B (0.88 g, 2.24 mmol) was dissolved in 4 mL of 4N HCl/dioxane and the mixture stirred overnight and concentrated. The residue was dissolved in 5 mL of acetonitrile and diisopropylethylamine (0.80 ml, 4.48 mmol) was added. The mixture was stirred for 1 hour at room temperature and 4 days at 65°C. The mixture was cooled to room temperature, diluted with water and extracted with 3 portions of ethyl ether. The combined organic extracts were washed with 1M aqueous phosphoric acid, water, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (30 g, 40% - 100% ethyl acetate/hexanes) to provide 0.35 g (65%) of the title compound. MS (DCI, NH₃): 244 (MH⁺); 261 (M+NH₄)⁺.

Example 1111D5(R)-cyclohexylmethyloxymethyl-thiomorpholine

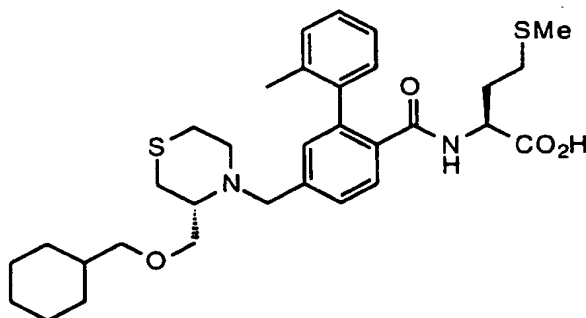
7840 Following the procedure of example 1178F, example 1111C (0.34 g, 1.40 mmol) provided 0.34 g (100%) of the title compound. MS (DCI, NH₃): 230 (MH⁺).



7845 Example 1111E

N-[4-(3-(R)cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine, methyl ester

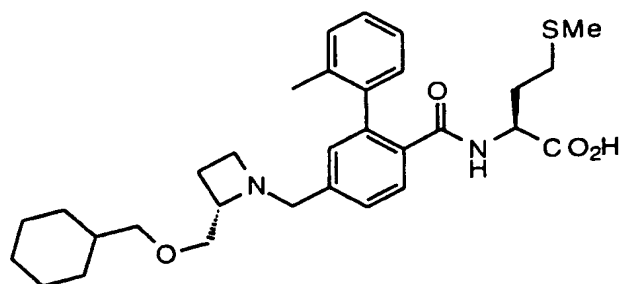
Following the procedure of example 1103C, example 1111D (172 mg, 0.75 mmol)
 was converted to 67 mg (11%) of the title compound. MS (ESI+): 599 (MH+); (ESI-):
 597 (M-H).



7855 Example 1111F

N-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine

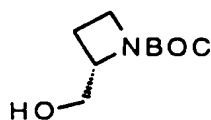
Following the procedure of example 1104D, the title compound was prepared. ¹H
 nmr (300 MHz., CD₃OD): δ 7.65, d, 1H; 7.48, d, 1H; 7.14 - 7.32, m, 5H; 4.40, m, 1H;
 4.10, d, 1H; 3.91, d, 1H; 3.80, dt, 1H; 3.24, dd, 2H; 3.16, m, 2H; 2.84, m, 2H; 2.56 -
 2.77, m, 3H; 2.05 - 2.13, m, 5H; 2.00, s, 3H; 1.93, m, 2H; 1.69, m, 6H; 1.55, m, 1H;
 1.09 - 1.32, m, 4H; 0.94, m, 2H. MS (ESI+): 585 (MH+); (ESI-): 583 (M-H). Calc'd
 for C₃₂H₄₀N₂O₄S₂•0.30 H₂O; C 65.12; H 7.62; N 4.75; Found: C 65.14; H 7.72; N
 4.60.



7865

Example 1114

N-[4-(2(S)-cyclohexylmethoxymethylazetidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

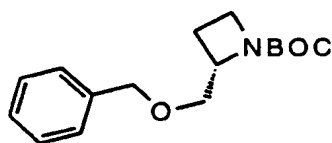


7870

Example 1114AN-t-Butoxycarbonyl-2(S)-hydroxymethylazetidine

Azetidine-2-carboxylic acid (1.25 g, 12.4 mmol) was dissolved in 10 mL of 2M aqueous sodium carbonate and a solution of di-tert-butylidicarbonate in 10 mL of THF was added and the mixture was stirred overnight. The mixture was diluted with water and ether and the layers were separated. The ether layer was washed with water and pH of the combined aqueous phases adjusted to ~ 2 with phosphoric acid. The mixture was extracted with 4 portions of 20% isopropanol/chloroform and the combined organic phases were dried, filtered and concentrated. The residue was dissolved in 15 mL of THF and cooled in an ice bath. The solution was treated with 25 mL of borane in THF (1M, 25 mmol) and stirring was continued for 1 hour. The ice bath was removed and the solution stirred for 2 hours and then quenched by the careful addition of 25 mL of 4:1 THF/water. The mixture was stirred for 15 minutes, carefully treated with 25 mL of 1N aqueous HCl, and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted with 2 additional portions of ethyl acetate. The combined organic fractions were washed with 2M aqueous sodium carbonate, water, brine, and dried, filtered and concentrated to provide 2.18 g (94%) of the title compound. MS (DCI, NH₃): 188 (MH⁺).

7885

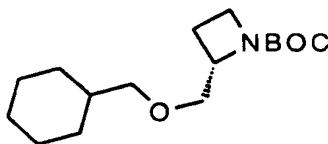


7890

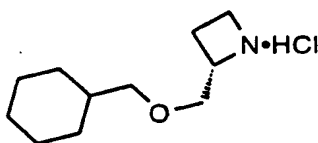
Example 1114B

N-t-Butoxycarbonyl-2(S)-benzyloxymethylazetidine

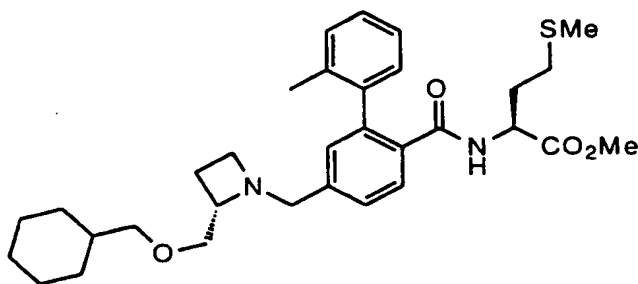
Following the procedure of example 1109F, example 1114A (0.94 g, 5 mmol) was converted to the crude product. The crude residue was purified by chromatography on silica gel (50 g, 20% ethyl acetate/hexanes) to provide 0.44 g, (32%) of the title compound. MS (DCI, NH₃): 278 (MH⁺).

Example 1114CN-t-Butoxycarbonyl-2(S)-cyclohexylmethyloxymethylazetidine

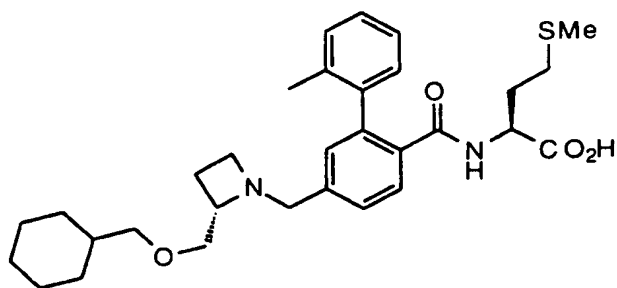
Following the procedure described in example 1109G, example 1114B (0.43 g, 1.56 mmol) provided 0.42 g, (95%) of the title compound. MS (DCI, NH₃): 284 (MH⁺).

Example 1114D2(S)-cyclohexylmethyloxymethylazetidine, hydrochloride salt

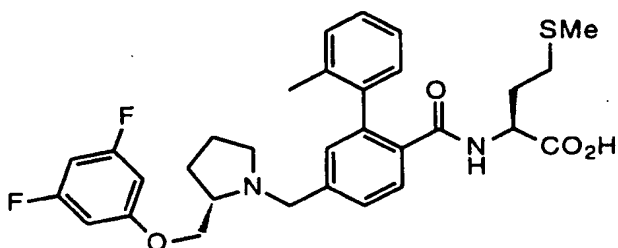
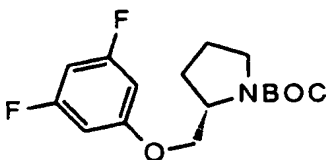
Following the procedure described in example 1106C, example 1114C (0.42 g, 1.48 mmol) was converted to 0.32 g (100%) of the title compound. MS (DCI, NH₃): 184 (MH⁺).

Example 1114EN-[4-(2(S)-cyclohexylmethyloxymethylazetidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Following the procedure described in example 1106D, part 1, example 1114D (220 mg, 1.0 mmol) provided 145 mg (53%) of the title compound. MS (ESI⁺): 553 (MH⁺); (ESI⁻): 551 (M-H).

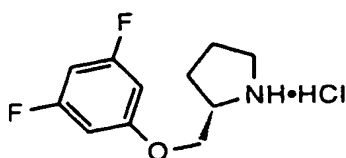
**Example 1114F****N-[4-(2(S)-cyclohexylmethoxymethylazetidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine**

Following the procedure of example 1104D, example 114E (100 mg, 0.18 mmol) provided 92 mg (95%) of the title compound. ¹H nmr (300 MHz., dmso d6): δ 8.10, bd, 1H; 7.47, d, 1H; 7.33, d, 1H; 7.20, m, 2H; 7.11, m, 3H; 4.21, m, 1H; 3.83, d, 1H; 3.54, d, 1H; envelope 3.07 - 3.48, m, 4H; 2.84, m, 1H; 1.98 - 2.22, m, 5H; 1.97, s, 3H; envelope, 0.77 - 1.95, 17H. MS (ESI+): 539 (MH+); (ESI-): 537 (M-H). Calc'd for C₃₁H₄₂N₂O₄S•0.90 H₂O; C 67.09; H 7.96; N 5.05; Found: C 67.09; H 7.84; N 5.00.

**Example 1115****N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine****Example 1115A****N-t-Butoxycarbonyl-2-(S)-(3,5-difluorophenoxy)pyrrolidine**

A solution of N-t-butoxycarbonyl-2-hydroxymethylpyrrolidine (0.40 g, 2.00 mmol), triphenylphosphine (1.05 g, 4.00 mmol), and 3,5-difluorophenol (0.52 g, 4.00

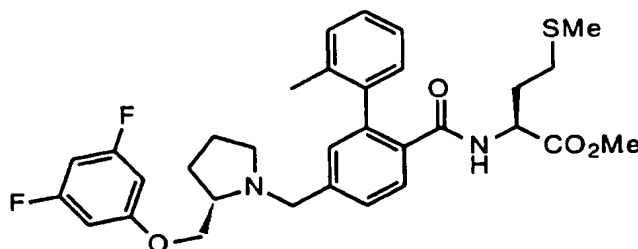
7940 mmol) in 5 mL of 1,2-dichloroethane was cooled in an ice bath and treated with a solution
 of diethylazodicarboxylate (0.63 mL, 4.00 mmol) in 3 mL of toluene. The cooling bath was
 removed and the solution was stirred for 70 hours at ambient temperature. The mixture was
 diluted with ether and extracted with 4N aqueous sodium hydroxide, dried, filtered and
 concentrated. The residue was purified by column chromatography on silica gel (30 g, 10%
 7945 ethyl acetate/hexanes) provided 0.49 g, (80%) of the title compound. MS (DCI, NH₃): 314
 (MH⁺).



Example 1115B

7950 2(S)-(3,5-difluorophenoxy)pyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1115A (0.48 g, 1.53 mmol)
 was provided 0.35 g (91%) of the title compound. MS (DCI, NH₃): 214 (MH⁺); 231
 (M+NH₄)⁺.

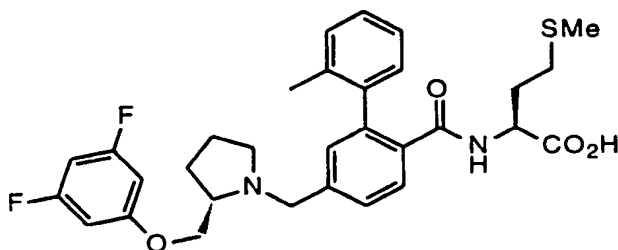


7955

Example 1115C

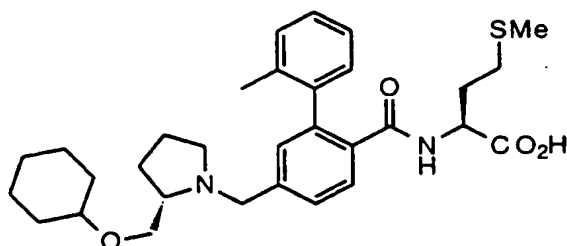
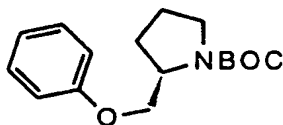
N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

7960 Following the procedure of example 1106C, part 1, example 1115B (0.19 g, 0.75
 mmol) provided 0.22 g (76%) of the title compound. MS (ESI⁺): 583 (MH⁺); (ESI⁻):
 581 (M-H).

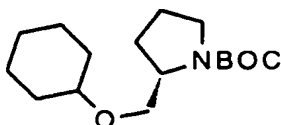


Example 1115DN-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-yl)methyl)-2-(2-methylphenyl)benzoyl]methionine

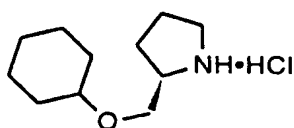
Following the procedure of example 1104D, example 1115C (0.21 g, 0.36 mmol) provided the title compound. ¹H nmr (300 MHz., CD₃OD): δ 7.69, d, 1H; 7.53, dd, 1H; 7.33, m, 1H; 7.05 - 7.29, m, 4H; 6.48 - 6.62, m, 3H; 4.48, m, 1H; 4.34, m, 1H; 4.12, m, 3H; 3.65, m, 1H; 3.31, m, 1H; 2.96, m, 1H; envelope 1.82 - 2.41, 13H; 1.68, m, 1H. MS (ESI+): 569 (MH⁺); (ESI-): 567 (M-H). Calc'd for C₃₁H₃₄F₂N₂O₄S•0.35 H₂O; C 64.76; H 6.08; N 4.87; Found: C 64.72; H 5.97; N 4.75.

Example 1116N-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-yl)methyl)-2-(2-methylphenyl)benzoyl]methionineExample 1116AN-t-Butoxycarbonyl-2(S)-phenoxymethylpyrrolidine

Following the procedure of example 1115 A, N-t-butoxycarbonyl-2-hydroxymethylpyrrolidine (0.80 g, 4.00 mmol) and phenol (1.13 g, 12.00 mmol) provided 0.99 g (89%) of the title compound. MS (DCI, NH₃): 278 (MH⁺).

Example 1116BN-t-Butoxycarbonyl-2(S)-cyclohexyloxymethylpyrrolidine

7990 Following the procedure of example 1109G, example 1116A (0.56 g, 2.00 mmol) provided 0.55 g (96%) of the title compound. MS (DCI, NH₃): 284 (MH⁺).



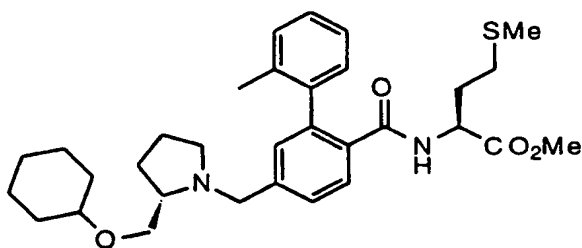
7995

Example 1116C

2-(S)-cyclohexyloxymethylpyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1116B (0.54 g, 1.90 mmol) provided 0.41 g (99%) of the title compound. MS (DCI, NH₃): 184 (MH⁺); 201 (M+NH₄)⁺.

8000

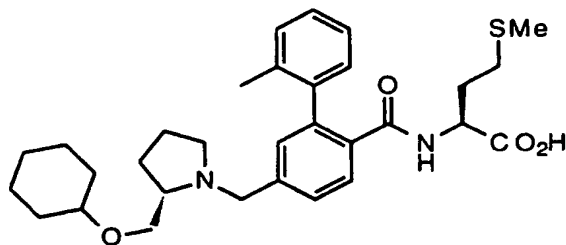


Example 1116D

N-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

8005

Following the procedure of example 1106D, part 1, example 1116C (0.22 g, 1.00 mmol) provided 0.22 g (83%) of the title compound. MS (ESI⁺): 553 (MH⁺); (ESI⁻): 551 (M-H).



8010

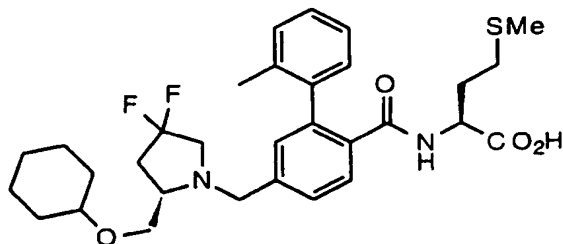
Example 1116E

N-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 1116D (0.22 g, 0.40 mmol) provided 0.18 g (81%). ¹H nmr (300 MHz., dmso d₆): δ 8.09, bd, 1H; 7.48, d, 1H; 7.36,

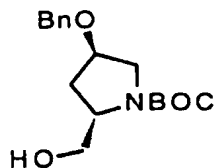
8015 d, 1H; 7.21, m, 2H; 7.13, m, 3H; 4.21, m, 2H; 3.49, d, 1H; envelope 3.15 - 3.45, 3H; 2.84, m, 1H; 2.70, m, 1H; 2.00 - 2.29, m, 7H; 1.96, s, 3H; 1.34 - 1.94, m, 8H; 1.18, m, 6H. MS (ESI+): 539 (MH+); (ESI-): 537 (M-H). Calc'd for $C_{31}H_{42}N_2O_4S \cdot 0.50 H_2O$: C 67.98; H 7.91; N 5.11; Found: C 67.95; H 7.81; N 5.05.

8020

Example 1117

N-[4-(2(S)-cyclohexylmethyloxymethyl)-4,4-difluoropyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoylmethionine

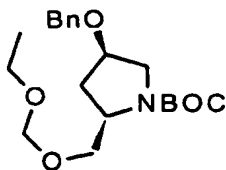
8025

Example 1117A

N-t-butoxycarbonyl-2(S)-hydroxymethyl-4(R)-benzyloxypyrrolidine

8030 A solution of trans-N-t-butoxycarbonyl-4-benzyloxy-L-proline (3.32 g, 10.3 mmol) in 20 mL of THF was cooled in an ice/acetone bath and a solution of borane in THF (1M, 20.6 mL, 20.6 mmol) was added dropwise. The solution was stirred for 2 hours then the cooling bath was removed and the mixture stirred overnight. The reaction was quenched by the careful addition of water followed by the addition of 20 mL of 1N aqueous HCl and then poured into ethyl acetate. The layers were separated and the aqueous layer extracted with 2 portions of ethyl acetate. The combined organic extracts were 2M aqueous sodium carbonate, water and brine, dried, filtered and concentrated to provide 3.19 g (100%) of the title compound. MS (DCI, NH_3): 308 (MH+).

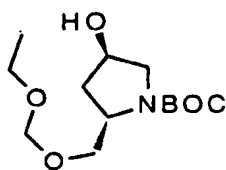
8035



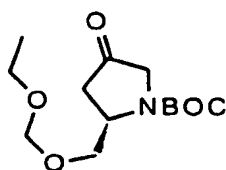
8040

Example 1117BN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4(R)-benzyloxypyrrolidine

A solution of example 1117A (2.14 g, 7.00 mmol) in 15 mL of methylene chloride was cooled in an ice bath and treated with diisopropylethylamine (1.87 mL, 10.50 mmol) followed by the addition of chloromethylethyl ether (0.97 mL, 10.50 mmol). The cooling bath was removed, the mixture stirred for 24 hours and then poured into 100 mL of ethyl ether. The organic phase washed with water, aqueous HCl, brine, dried, filtered and concentrated to provide 2.32 g (94%) of the title compound. MS (DCI, NH₃): 366 (M + NH₄)⁺.

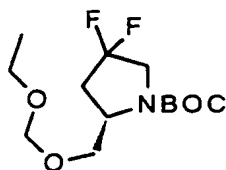
Example 1117CN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4(R)-hydroxypyrrolidine

A solution of example 1117B (2.29 g, 6.50 mmol) in 20 mL of degassed methanol was treated with Perleman's catalyst (0.40 g) and then the mixture was stirred under a balloon of hydrogen gas overnight. The mixture was diluted with ethyl acetate and filtered through a plug of silica gel. The silica gel plug was washed well with ethyl acetate and the filtrate concentrated to provide 1.77 g (99%) of the title compound. MS (DCI, NH₃): 276 (MH⁺).

Example 1117DN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4-oxopyrrolidine

A solution of example 1117C (0.99 g, 3.59 mmol) in 20 mL of 10% acetonitrile/methylene chloride was treated with powdered, activated 4Å molecular sieves (1 g), 4-methylmorpholine-4-oxide (0.63 g, 5.38 mmol) and the mixture stirred for 30 minutes. The suspension was treated with tetrapropylammonium perruthenate (0.04g, 0.11 mmol) and the resulting black mixture stirred for 30 minutes. The mixture was treated with ~ 3 g of celite and diluted with 30 mL of ether and stirred for 20 minutes. The suspension was then filtered through a pad of silica gel (which was washed well with ether) and the

filtrate concentrated to provide 0.91 g (93%) of the title compound. MS (DCI, NH₃): 274 (MH⁺); 291 (M+NH₄)⁺.

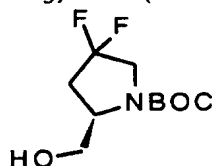


8075

Example 1117EN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4,4--difluoropyrrolidine

A solution of example 1117D (0.90 g, 3.30 mmol) in 20 mL of methylene chloride was cooled in an dry ice/acetone bath and treated with DAST (1.80 mL, 13.20 mmol). The bath was removed and the mixture stirred for 48 hours, cooled in an ice bath and carefully quenched by the addition of 2M aqueous sodium carbonate. The layers were separated and the aqueous layer was extracted with 2 additional portions of methylene chloride and the combined organic fractions were dried, filtered and concentrate. The residue was purified by column chromatography on silica gel (40 g, 15% ethyl acetate/hexanes) provided 0.70 g (72%) of the title compound. MS (DCI, NH₃): 296 (MH⁺); 313 (M+NH₄)⁺.

8080



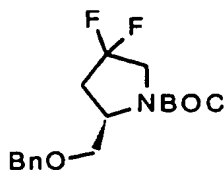
8085

Example 1117FN-t-butoxycarbonyl-2(S)-hydroxymethyl-4,4--difluoropyrrolidine

A solution of example 1117E (0.69 g, 2.30 mmol) in 10 mL of methanol was treated with 0.5 mL of concentrated aqueous HCl and the mixture stirred overnight. The yellow solution was poured into 2M aqueous sodium carbonate and concentrated to remove the methanol. The mixture was diluted with THF and ~1 g of di-t-butylidicarbonate was added and the mixture stirred for 3 hours and diluted with ethyl ether. The phases were separated and the aqueous phase was extracted with 3 portions of methylene chloride. The combined organic phases were dried, filtered and concentrated to provide 0.48 g (88%) of the title compound. MS (DCI, NH₃): 238 (MH⁺); 255 (M+NH₄)⁺.

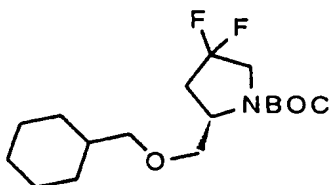
8090

8095

Example 1117G

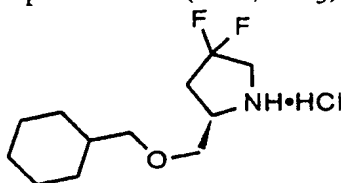
N-t-butoxycarbonyl-2(S)-benzyloxymethyl-4,4--difluoropyrrolidine

8100 Following the procedure of example 1109F, example 1117G (0.24 g, 1.00 mmol) provided 0.26 g (78%) of the title compound. MS (DCI, NH₃): 328 (MH⁺).

Example 1117H

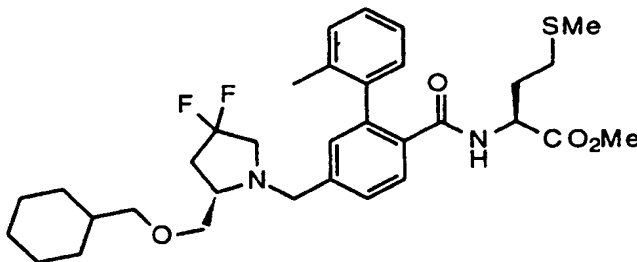
8105 N-t-butoxycarbonyl-2(S)-cyclohexylmethyloxymethyl-4,4--difluoropyrrolidine

Following the procedure of example 1109G, example 1117G (0.25 g, 1.10 mmol) provided 0.22 g (87%) of the title compound. MS (DCI, NH₃): 334 (MH⁺).

Example 1117I

8110 2(S)-cyclohexylmethyloxymethyl-4,4--difluoropyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1117H (0.22 g, 0.92 mmol) provided 0.17 g (98%) of the title compound. MS (DCI, NH₃): 234 (MH⁺).



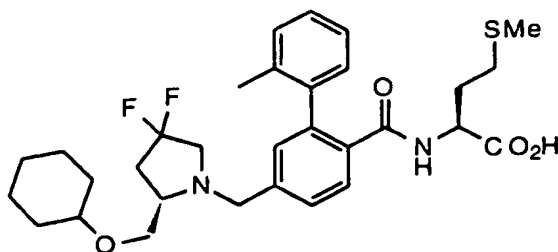
8115

Example 1117J

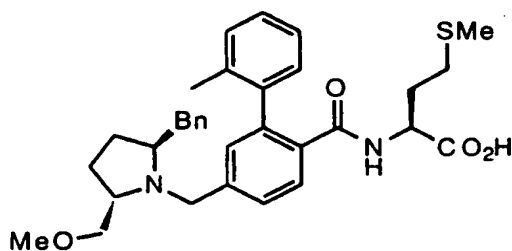
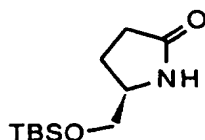
N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Following the procedure of example 1106D, part 1, example 1117I (0.16 g, 0.60 mmol) provided 0.13 g (43%) of the title compound. MS (ESI⁺): 603 (MH⁺); (ESI⁻): 601 (M-H).

8120

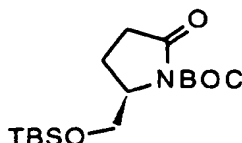
**Example 1117K****N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine**

Following the procedure of example 1104D, example 1117J (123 mg, 0.20 mmol) provided 116 mg (98%) of the title compound. ¹H nmr (300 MHz., CD₃OD): δ 7.62, d, 1H; 7.43, d, 1H; 7.13 - 7.32, m, 5H; 4.44, m, 1H; 4.26, d, 1H; 3.56, d, 1H; 3.54, dd, 1H; 3.48, dd, 1H; 3.24, m, 2H; 3.10, m, 1H; 2.71, m, 1H; 2.37, m, 1H; 2.03 - 2.25, m, 6H; 2.00, s, 3H; 1.87 - 2.00, m, 1H; 1.68, m, 5H; 1.53, m, 1H; 1.18, m, 3H; 0.90, m, 2H. MS (ESI+): 589 (MH+); (ESI-): 587 (M-H). Calc'd for C₃₂H₄₂F₂N₂O₄S; C 65.28; H 7.19; N 4.76; Found: C 64.99; H 7.16; N 4.54.

**Example 1118****N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine****Example 1118A****5(S)-t-butyltrimethylsilyloxymethyl-2-pyrrolidinone**

A stirred solution of 5(S)-hydroxymethyl-2-pyrrolidinone (5.00 g, 0.043 mol) in 20 mL of DMF was treated with imidazole (6.81 g, .10 mol) and then t-butyltrimethylchlorosilane (7.20 g, 0.047 mol) and the mixture stirred for 2 hours. The thick

mixture was diluted with water and extracted with 3 portions of ethyl acetate. The combined ethyl acetate layer were washed with water, brine, dried filtered and concentrated to provide 7.50 g (75%) of the title compound. MS (DCI, NH₃): 230 (MH⁺); 247 (M+NH₄)⁺.



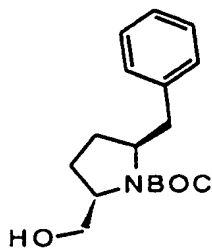
8150

Example 1118B

N-t-butoxycarbonyl-5(S)-t-butyltrimethylsilyloxymethyl-2-pyrrolidinone

8155 A stirred solution of example 1118A (1.65 g, 7.20 mmol) in 5 mL of acetonitrile at rt was treated with DMAP (0.15 g, 1.25 mmol) and di-tert-butyl dicarbonate (1.09 g, 7.20 mmol) and the mixture stirred at ambient temperature for 48 hours at which time an additional 0.80 g of di-tert-butyl dicarbonate was added. The mixture was stirred an additional 6 hours and then diluted with 80 mL of ether and washed with 1M aqueous phosphoric acid, water, brine, dried filtered and concentrated. The residue was purified by column chromatography on silica gel (100 g, 15% ethyl acetate/hexanes) to provide 1.50 g (63%) of the title compound.

8160 MS (DCI, NH₃): 347 (M+NH₄)⁺.



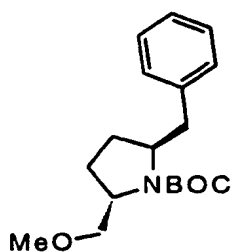
Example 1118C

N-t-butoxycarbonyl-2(S)-hydroxymethyl-5(S)-benzylpyrrolidine

8165 A solution of example 1118C (1.05 g, 3.17 mmol) in 10 mL of toluene was cooled in a dry ice/acetone bath and treated with diisobutylaluminum hydride (3.2 mL of a 1.5M solution in toluene, 4.75 mmol) and the mixture stirred for 1 hour. The dry ice bath was replaced with an ice/acetone bath and the mixture stirred for an additional hour and then quenched with the careful addition of methanol (0.25 mL) and stirring continued until the evolution of gas ceased. The solution was then treated with 1N aqueous HCl and ethyl acetate and the mixture stirred until 2 clear phases resulted. The aqueous layer was extracted with ethyl acetate and the combined organic fractions were washed with 1N HCl, saturated sodium bicarbonate, brine, dried, filtered and concentrated. The residue was dissolved in 10 mL of methylene chloride and cooled in a dry ice/acetone bath and then treated with boron

8170

8175 trifluoride etherate (0.41 mL, 3.34 mmol) followed by benzylmagnesium chloride (4 mL of a
2.0M solution in THF, 8.00 mmol) and the mixture stirred for 1.5 hours and quenched by
the addition of saturated sodium bicarbonate. The cooling bath was removed and the mixture
allowed to reach room temperature. The mixture was diluted with ether and extracted with
8180 ether and the combined organic extracts dried, filtered and concentrated. The residue was
diluted with THF (10 mL) and treated with TBAF (10 mL of a 1.0M THF solution, 10.0
mmol) and the mixture stirred overnight. The mixture was diluted with water and extracted
with 3 portions of ethyl acetate. The combined organic fractions were washed with water,
brine, dried, filtered and concentrated. The residue was purified by column chromatography
8185 on silica gel (50 g, 30% ethyl acetate/hexanes) to provide 0.15 g (16%) of the title
compound. MS (DCI, NH₃): 292 (MH)⁺.

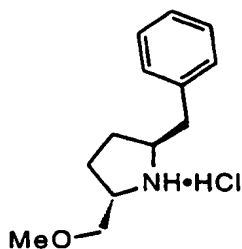


Example 1118D

8190 N-t-butoxycarbonyl-2(S)-methoxymethyl-5-benzylpyrrolidine

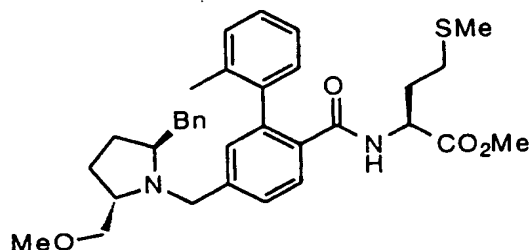
A solution of example 1118C (224 mg, 0.77 mmol) in 1 mL of DMF was treated with
methyl iodide (96 μ L, 1.54 mmol) and cooled in an ice bath. The mixture was treated with
sodium hydride (60%, 62 mg, 1.54 mmol) and after 10 minutes the cooling bath removed
and stirring continued for 2 hours. The reaction was quenched by the addition of water and
8195 the mixture diluted with water and extracted with 3 portions of ethyl ether. The combined
organic fractions were washed with water, brine, dried, filtered and concentrated. The
residue was purified by column chromatography on silica gel (20 g, 20% ethyl
acetate/hexane) to provide 158 mg (67%) of the title compound. MS (DCI, NH₃): 306
(MH)⁺.

8200



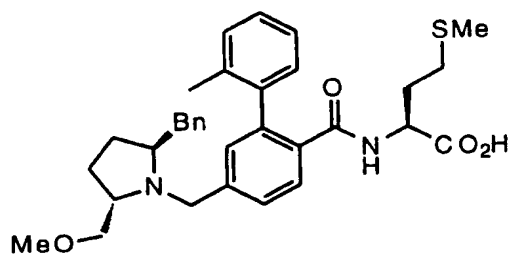
Example 1118E2(S)-methoxymethyl-5-benzylpyrrolidine, hydrochloride salt

8205 Following the procedure of example 1106C, example 1118D (152 mg, 0.5 mmol) provided 110 mg, (91%) of the title compound. MS (DCI, NH₃): 306 (MH)⁺.

Example 1118F

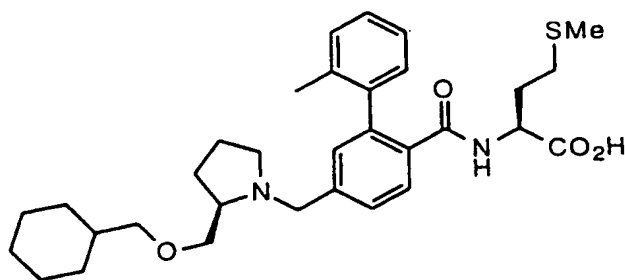
8210 N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Following the procedure of example 1106D, part 1, example 1118E (106 mg, 0.44 mmol) provided 95 mg (41%) of the title compound. MS (ESI⁺): 575 (MH⁺); (ESI⁻): 573 (M-H).

Example 1118G

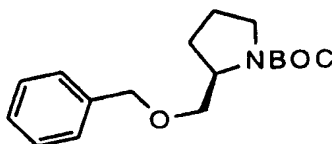
8215 N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

8220 Following the procedure of example 1105D, example 1118F (88 mg, 0.15 mmol) provided 50 mg (60%) of the title compound. ¹H nmr (300 MHz., dmsO d₆): δ 8.11, d, 1H; 7.48, m, 2H; 7.19, m, 8H; 7.03, d, 2H; 4.22, m, 1H; 4.08, d, 1H; 3.93, d, 1H; 3.22, s, 3H; 3.09, m, 2H; 2.94, dd, 1H; 2.37, dd, 1H; 1.99 - .22, m, 4H; 1.97, s, 3H; 1.78, bm, 2H; 1.56, m, 2H; 1.42, m, 2H. MS (ESI⁺): 561 (MH⁺); (ESI⁻): 559 (M-H). Calc'd for C₃₃H₄₀N₂O₄S•0.43 H₂O; C 69.72; H 7.24; N 4.93; Found: C 69.72; H 7.11; N 4.78.

Example 1119

N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

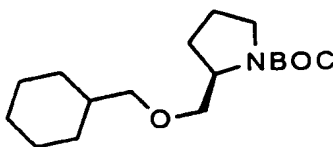
8230

Example 1119A

N-t-Butoxycarbonyl- 2(R)-benzyloxymethylpyrrolidine

8235

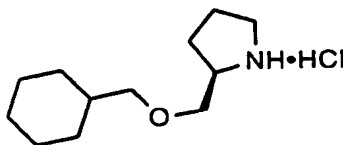
Following the procedure of example 1109F, N-t-butoxycarbonyl-2(R)-hydroxymethylpyrrolidine (1.06 g, 5.00 mmol) provided 1.20 g (82%) of the title compound. MS (DCI, NH₃): 292 (MH)⁺.

Example 1119B

N-t-Butoxycarbonyl- 2(R)-cyclohexylmethoxymethylpyrrolidine

8240

Following the procedure of example 1109G, example 1119A (0.60 g, 2.06 mmol) provided 0.59 g (97%) of the title compound. MS (DCI, NH₃): 298 (MH)⁺.

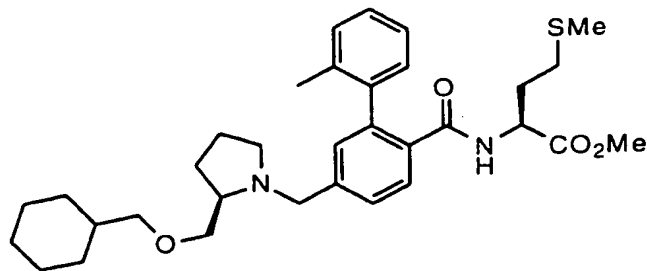
Example 1119C

2(R)-cyclohexylmethoxymethylpyrrolidine, hydrochloride salt

8245

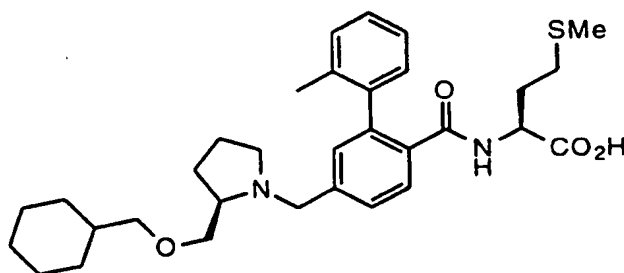
Following the procedure of example 1106C, example 1119B (573 mg, 1.93 mmol) provided 467 mg (100%) of the title compound. MS (DCI, NH₃): 198 (MH)⁺.

8250

Example 1119D

N-[4-(2-cyclohexylmethoxymethyl)pyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

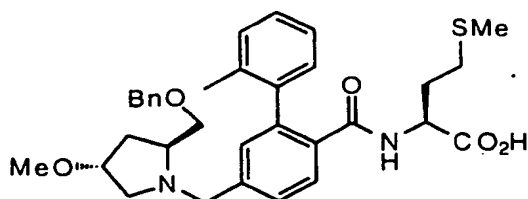
8255 Following the procedure of example 1106C, example 1119C (175 mg, 0.75 mmol) provided 181 mg (64%) of the title compound. MS (ESI+): 567 (MH+); (ESI-): 565 (M-H).

Example 1119E

N-[4-(2-cyclohexylmethoxymethyl)pyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoyl]methionine

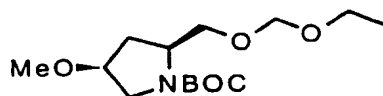
8260 Following the procedure of example 1104D, example 1119D (174 mg, 0.31 mmol) provided 163 mg (95%) of the title compound.. ¹H nmr (300 MHz., dmsd d6): δ 8.10, d, 1H; 7.47, d, 1H; 7.36, d, 1H; 7.20, m, 2H; 7.11, m, 3H; 4.21, m, 1H; 4.17, d, 1H; 3.48, d, 1H; 3.18, m, 2H; 2.85, m, 1H; 2.76, m, 1H; 1.98 - 2.30, m, 7H; 1.97, s, 3H; 1.70 - 1.90, m, 3H; 1.62, m, 7H; 1.49, m, 2H; 1.10, m, 4H; 0.88, m, 2H. MS (ESI+): 553 (MH+); (ESI-): 551 (M-H). Calc'd for C₃₂H₄₄N₂O₄S•0.50 H₂O; C 68.42; H 8.07; N 4.99; Found: C 68.47; H 7.82; N 4.77.

8270

Example 1120

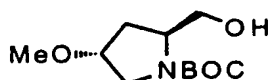
N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8275

Example 1120A

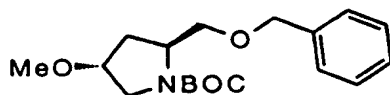
N-t-Butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4(R)-methoxypyrrolidine

8280 Following the procedure of example 1118D, example 1117C (0.76g, 2.76 mmol) provided 0.64 g (80%) of the title compound. MS (DCI, NH₃): 290 (MH)⁺.

Example 1120B

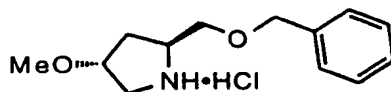
8285 N-t-Butoxycarbonyl-2(S)-hydroxymethyl-4(R)-methoxypyrrolidine

Following the procedure of example 1117F, example 1120A (0.64g, 2.21 mmol) provided 0.39 g (77%) of the title compound. MS (DCI, NH₃): 232 (MH)⁺.

Example 1120C

8290 N-t-Butoxycarbonyl-2(S)-Benzyloxymethyl-4(R)-methoxypyrrolidine

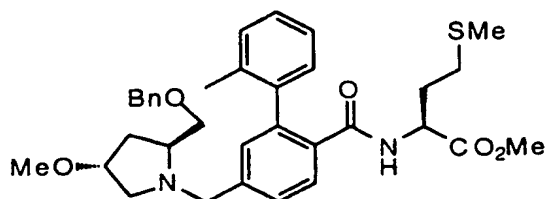
Following the procedure of example 1109F, example 1120B (0.39 g, 1.68 mmol) provided 0.42 g (78%) of the title compound. MS (DCI, NH₃): 332 (MH)⁺.

Example 1120D

8295 2(S)-Benzyloxymethyl-4(R)-methoxypyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1120C (0.41 g, 1.28 mmol) provided 0.32 g (97%) of the title compound. MS (DCI, NH₃): 232 (MH)⁺.

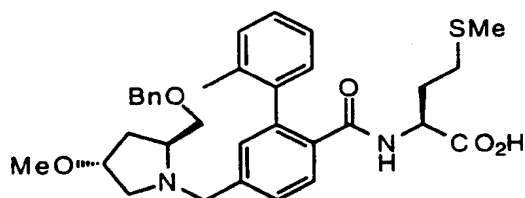
8300

Example 1120E

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoylmethionine, methyl ester

8305

Following the procedure of example 1106D, part 1, example 1120D (0.26 g, 1.00 mmol) provided 0.21 g (70%) of the title compound. MS (ESI⁺): 591 (MH⁺); (ESI⁻): 589 (M-H).

Example 1120F

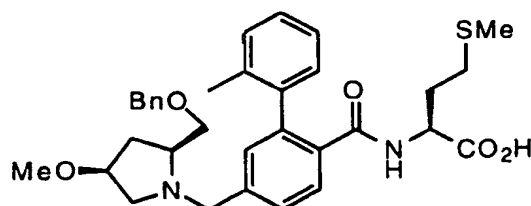
N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoylmethionine

8310

Following the procedure of example 1104D, example 1120E (197 mg, 0.33 mmol) provided 163 mg (86%) of the title compound. ¹H nmr (300 MHz., dmsO d₆): δ 8.12, d, 1H; 7.48, d, 1H; 7.36, dd, 1H; 7.27, m, 5H; 7.20, m, 2H; 7.13, m, 3H; 4.48, s, 2H; 4.21, m, 2H; 3.82, m, 1H; 3.53, m, 2H; 3.42, m, 2H; 3.14, s, 3H; 1.99 - 2.30, m, 6H; 1.96, s, 3H; 1.64 - 1.90, m, 4H. MS (ESI⁺): 577 (MH⁺); (ESI⁻): 575 (M-H). Calc'd for C₃₃H₄₀N₂O₅S•0.55 H₂O; C 67.56; H 7.06; N 4.77; Found: C 67.56; H 7.02; N 4.80.

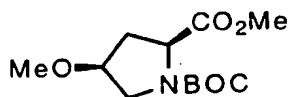
8315

8320

Example 1121

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

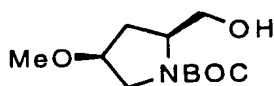
8325



Example 1121A

N-t-Butoxycarbonyl-4(S)-methoxy-L-proline, methyl ester

8330 Following the procedure of example 1118D, N-t-butoxycarbonyl-4(S)-hydroxy-L-proline, methyl ester (1.22 g, 5.00 mmol) provided 1.04 g (80%) of the title compound. MS (DCI, NH₃): 260 (MH⁺); 277 (M+NH₄)⁺.

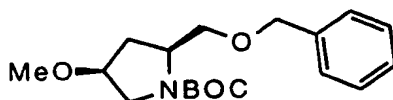


Example 1121B

8335

N-t-Butoxycarbonyl-2(S)-hydroxymethyl-4(S)-methoxypyrrolidine

Following the procedure of example 1109E, example 1121A (1.03 g, 3.97 mmol) provided 0.83 g (90%) of the title compound. MS (DCI, NH₃): 232 (MH⁺).

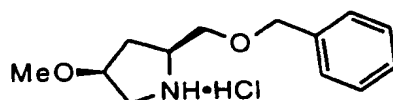


Example 1121C

8340

N-t-Butoxycarbonyl-2(S)-benzyloxymethyl-4(S)-methoxypyrrolidine

Following the procedure of example 1109F, example 1121B (0.41 g, 1.78 mmol) provided 0.46 g (80%) of the title compound. MS (DCI, NH₃): 322 (MH⁺).

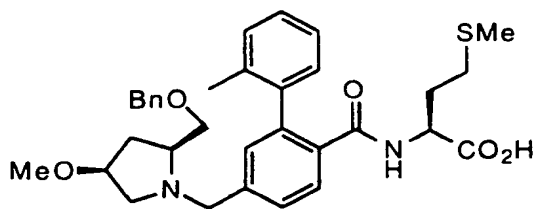


8345

Example 1121D

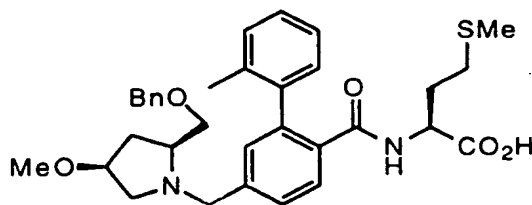
2(S)-benzyloxymethyl-4(S)-methoxypyrrolidine, hydrochloride salt

8350 Following the procedure of example 1106C, example 1121C (228 mg, 0.71 mmol) provided 183 mg (100%) of the title compound. MS (DCI, NH₃): 222 (MH⁺).

Example 1121E

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

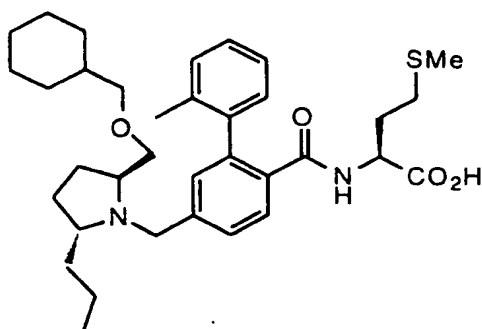
8355 Following the procedure of example 1106D, part 1, example 1121D (178 mg, 0.69 mmol) provided 210 mg (71%) of the title compound. MS (ESI+): 591 (MH+); (ESI-): 589 (M-H).

Example 1121F

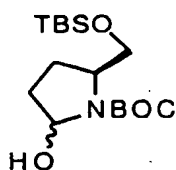
N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8365 Following the procedure used in example 1104D, example 1121E (204 mg, 0.34 mmol) provided 195 mg (99%) of the title compound. ¹H nmr (300 MHz., dmsO d6): δ 8.08, d, 1H; 7.45, d, 1H; 7.33, d, 1H; 7.28, m, 5H; 7.21, m, 2H; 7.14, m, 3H; 4.49, s, 2H; 4.22, m, 1H; 4.18, m, 1H; 3.79, m, 1H; 3.56, dd, 1H; 3.43, dd, 1H; 3.09, s, 3H; 2.90, d, 1H; 2.75, m, 1H; envelope 1.99 - 2.35, 11H; 1.97, s, 3H; 1.78, bm, 2H; 1.51, ddd, 1H. MS (ESI+): 577 (MH+); (ESI-): 575 (M-H). Calc'd for C₃₃H₄₀N₂O₅S•0.45 H₂O; C 67.77; H 7.05; N 4.79; Found: C 67.80; H 6.93; N 4.62.

8370

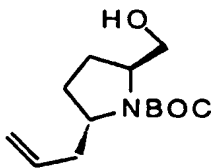
Example 1122

N-[4-(2-cyclohexyloxymethyl)-5-propylpyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoylmethionine

Example 1122A

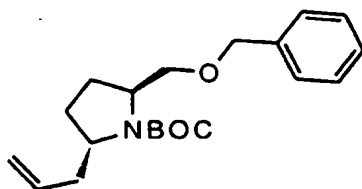
N-t-Butoxycarbonyl-2(R,S)-hydroxy-5(S)-t-butyltrimethylsilyloxymethylpyrrolidine

Example 1118B (3.10 g, 9.36 mmol) was dissolved in 20 mL of toluene and cooled in a dry ice/acetone bath. The cold solution was treated with diisobutylaluminum hydride (9.4 mL of a 1.5M toluene solution, 14.0 mmol), the dry ice bath was removed and the mixture stirred for 2 hours. The mixture was cooled in an ice/acetone bath and quenched by the careful addition of 10 mL of a 10% methanol/toluene solution. After the cessation of bubbling, the mixture was treated with 75 mL of 1N aqueous HCl and 100 mL of ether and vigorously stirred for 30 minutes and poured into a separatory funnel. The layers were separated and the aqueous layer was extracted with 2 portions of ether and the combined organic fractions were washed with 1N HCl, water and brine, dried, filtered and concentrated to provide 2.93 g (94%) of the title compound. MS (DCI, NH₃): 332 (MH⁺); 314 (M+NH₄)⁺ - H₂O.

Example 1122B

N-t-Butoxycarbonyl-5(S)-allyl-2(S)-hydroxymethylpyrrolidine

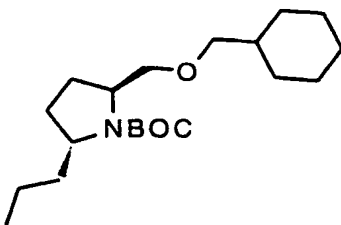
8395 A solution of example 1122A (663 mg, 2 mmol) and allyltrimethylsilane (1.2 mL, 8 mmol) in 12 mL methylene chloride was cooled in a dry ice/acetone bath and treated with boron trifluoride etherate (0.49 mL, 4.00 mmol) dropwise. The solution was stirred for 30 minutes and then the dry ice bath was replaced with an ice/acetone bath and the mixture stirred an additional 30 minutes and quenched by the addition of 2M sodium carbonate. The
8400 mixture was diluted with water and methylene chloride and the layers separated. The aqueous phase was extracted with 2 additional portions of methylene chloride and the combined organic fractions were dried, filtered and concentrated. The residue was dissolved in 4 mL of THF and treated with TBAF (4 mL of a 1.0M THF solution, 4 mmol) and the mixture stirred overnight. The reaction was partitioned between water and 3 portions of
8405 ethyl acetate. The combined organic extracts were washed with water, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (25 g, 30% ethyl acetate/hexanes) to provide 227 mg (47%) of the title compound. MS (DCI, NH₃): 242 (MH⁺).



8410 Example 1122C

N-t-Butoxycarbonyl-5(S)-allyl-2(S)-benzyloxymethylpyrrolidine

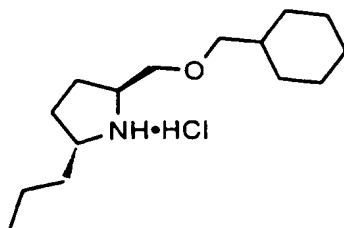
Following the procedure of example 1109F, example 1122B (223 mg, 0.92 mmol) provided 250 mg (82%) of the title compound. (DCI, NH₃): 332 (MH⁺).



8415 Example 1122D

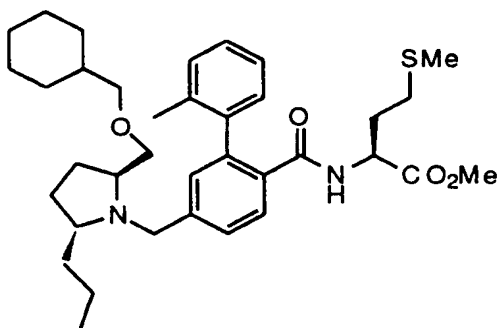
N-t-Butoxycarbonyl-5(R)-propyl-2(S)-cyclohexylmethyloxymethylpyrrolidine

Following the procedure of example 1109G, example 1122C (245 mg, 0.74 mmol) provided 246 mg (100%) of the title compound. (DCI, NH₃): 340 (MH⁺).

Example 1122E5(R)-propyl-2(S)-cyclohexylmethyloxymethylpyrrolidine, hydrochloride salt

8425

Following the procedure of example 1106C, example 1122D (245 mg, 0.74 mmol) provided 204 mg (100%) of the title compound. (DCI, NH₃): 240 (MH⁺).

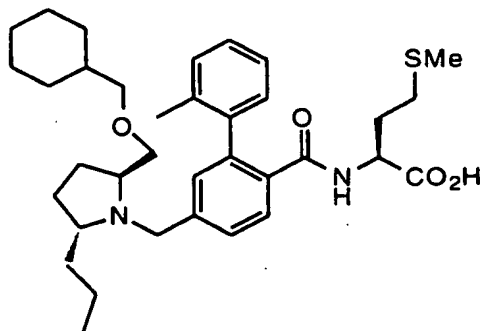
Example 1122F

8430

N-[4-(2(S)-cyclohexylmethyloxymethyl-5(R)-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

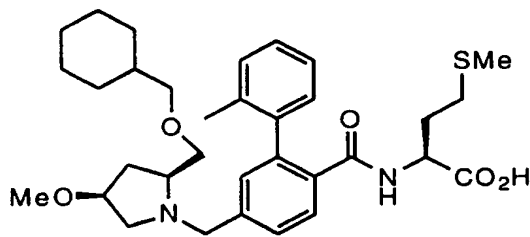
Following the procedure of example 1106D, part 1, example 1122E (204 mg, 0.74 mmol) provided 110 mg (36%) of the title compound. MS (ESI⁺): 609 (MH⁺): (ESI⁻): 607 (M-H).

8435

Example 1122G

N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

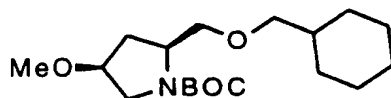
8440 Following the procedure of example 1104D, example 1122F (104 mg, 0.17 mmol) provided 87 mg (86%) of the title compound. ¹H nmr (300 MHz., dmso d6): δ 8.04, d, 1H; 7.46, d, 1H; 7.35, d, 1H; 7.20, m, 2H; 7.13, m, 3H; 4.22, m, 1H; 3.83, dd, 2H; 3.08, m, 2H; 3.04, d, 2H; 2.88, pentet, 1H; 2.63, m, 1H; 1.99 - 2.24, m, 6H; 1.96, s, 3H; 1.77, bm, 4H; 1.59, m, 6H; envelope 1.00 - 1.55, 11H; 0.81, m, 5H. MS (ESI+): 595 (MH+); (ESI-): 593 (M-H). Calc'd for C₃₅H₅₀N₂O₄S•0.55 H₂O; C 69.51; H 8.52; N 4.63; Found: C 69.54; H 8.32; N 4.58.



8450

Example 1123

N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

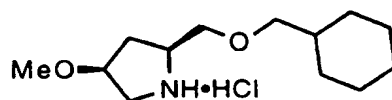


8455

Example 1123A

N-t-Butoxycarbonyl-2(S)-cyclohexylmethoxy-4(S)-methoxypyrrolidine

Following the procedure of example 1109G, example 1112C (227 mg, 0.71 mmol) provided 232 (100%) of the title compound. (DCI, NH₃): 328 (MH⁺).



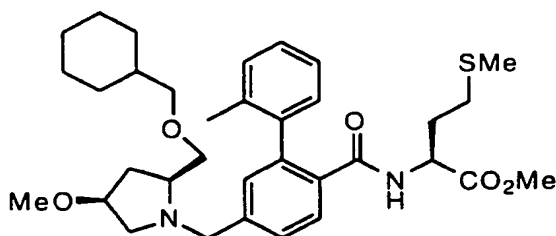
8460

Example 1123B

2(S)-cyclohexylmethoxy-4(S)-methoxypyrrolidine, hydrochloride salt

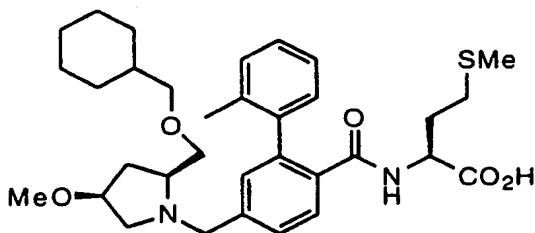
Following the procedure of example 1106C, example 1123 A (232 mg, 0.71 mmol) provided 187 mg (100%) of the title compound. (DCI, NH₃): 228 (MH⁺).

8465

Example 1123C

N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

8470 Following the procedure of example 1106D, part 1, example 1123B (181 mg, 0.69 mmol) provided 196 mg (66%) of the title compound. MS (ESI+): 597 (MH+): (ESI-): 595 (M-H).

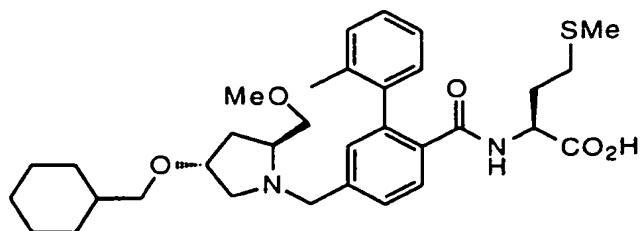
Example 1123D

N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

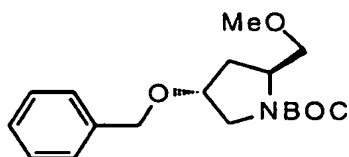
8475 Following the procedure of example 1104D, example 1123C (190 mg, 0.32 mmol) provided 174 mg (93%) of the title compound. ¹H nmr (300 MHz., dmso d6): δ 8.12, d, 1H; 7.46, d, 1H; 7.35, dd, 1H; 7.19, m, 2H; 7.13, m, 3H; 4.18, m, 2H; 3.78, m, 1H; 3.45, dd, 1H; 3.29, d, 1H; 3.17, dd, 1H; 3.15, dd, 1H; 3.08, s, 3H; 2.89, bd, 1H; 2.72, m, 1H; 2.29, m, 1H; envelope 1.97 - 2.25, 6H; 1.96, s, 3H; 1.77, bm, 2H; 1.62, m, 5H; 1.47, m, 2H; 1.12, m, 3H; 0.86, bq, 2H. MS (ESI+): 583 (MH+): (ESI-): 581 (M-H). Calc'd for C₃₃H₄₆N₂O₅SH₂O; C 68.01; H 7.96; N 4.81; Found: C 67.96; H 7.96; N 4.81.

8480

8485

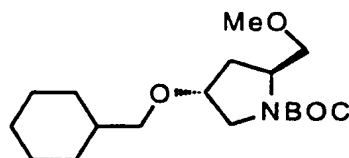
Example 1124

8490 N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

Example 1124A

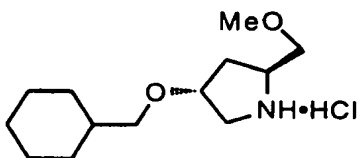
8495 N-t-Butoxycarbonyl-2(S)-methoxymethyl-4(S)-benzyloxypyrrolidine

Following the procedure of example 1118D, example 1117A (922 mg, 3.00 mmol) provided 0.64 g (67%) of the title compound. (DCI, NH₃): 322 (MH⁺).

Example 1124B

8500 N-t-Butoxycarbonyl-2(S)-methoxymethyl-4(S)-cyclohexylmethyloxypyrrolidine

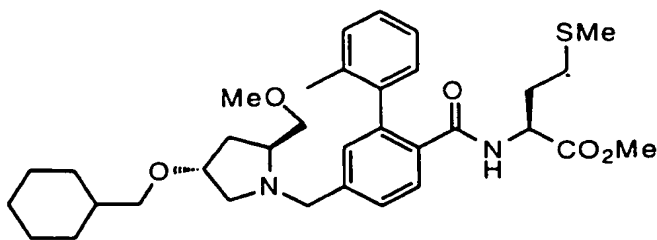
Following the procedure of example 1109G, example 1124A (0.63 g, 1.96 mmol) provided 0.63 g (99%) of the title compound. (DCI, NH₃): 328 (MH⁺).

Example 1124C

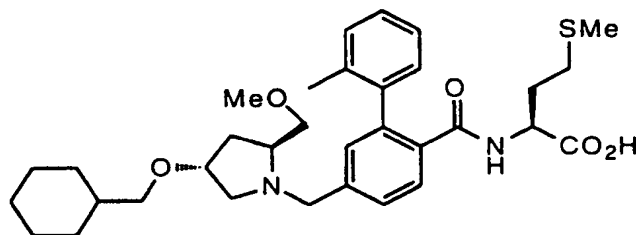
8505 2(S)-methoxymethyl-4(S)-cyclohexylmethyloxypyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1124B (627 mg, 1.91 mmol) provided 511 mg (101%) of the title compound. (DCI, NH₃): 228 (MH⁺).

8510

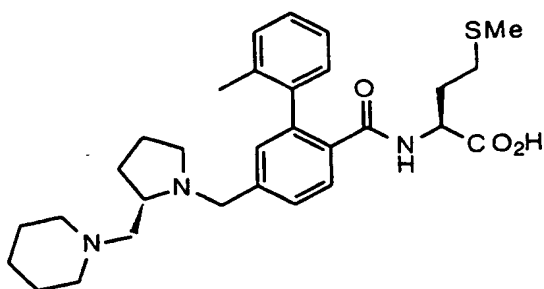
Example 1124DN-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoylmethionine, methyl ester

8515 Following the procedure of example 1106D, part 1, example 1124C (264 mg, 1.50 mmol) provided 209 mg (70%) of the title compound. MS (ESI+): 597 (MH+); (ESI-): 595 (M-H).

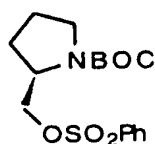
Example 1124EN-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoylmethionine

8520 Following the procedure of example 1104D, example 1124D (197 mg, 0.33 mmol) provided 176 mg (92%) of the title compound. ¹H nmr (300 MHz., dmso d6): δ 8.14, d, 1H; 7.47, d, 1H; 7.38, d, 1H; 7.22, m, 2H; 7.13, m, 3H; 4.23, m, 1H; 4.13, bd, 1H; 3.87, m, 1H; 3.55, bm, 1H; 3.42, dd, 2H; 3.27, dd, 1H; 3.23, s, 3H; 3.11, dd, 1H; ; envelope 1.98 - 2.24, 6H; 1.96, s, 3H; envelope 1.55 - 1.93, 8H; 1.43, bm, 1H; 1.12 - 1.30, m, 4H; 0.86, bq, 2H. MS (ESI+): 583 (MH+); (ESI-): 581 (M-H). Calc'd for C₃₃H₄₆N₂O₅S•0.50 H₂O; C 66.97; H 8.00; N 4.73; Found: C 67.04; H 7.97; N 4.51.

8530

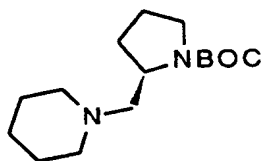
Example 1125

N-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Example 1125A

N-t-Butoxycarbonyl-2(S)-phenylsulfonyloxymethylpyrrolidine

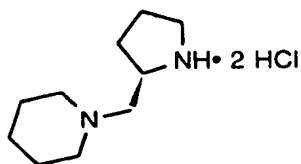
8540 A solution of N-t-Butoxycarbonyl-2(S)-hydroxymethylpyrrolidine (2.01 g, 10.00 mmol) and triethyl amine (1.70 mL, 12.00 mmol) in 10 mL of methylene chloride was cooled in an ice bath and treated with benzenesulfonylchloride (1.96 g, 11.00 mmol) and the mixture placed in a refrigerator overnight. The mixture was allowed to reach room temperature and partitioned between ethyl ether and water. The aqueous phase was extracted with ether and the combined organic layers washed with water 1N HCl, saturated sodium bicarbonate, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (120 g, 25% ethyl acetate/hexanes) to provide 2.82 g (83%) of the title compound. MS (DCI, NH₃): 359 (M+NH₄)⁺.

Example 1125B

N-t-Butoxycarbonyl-2(S)-piperidinylmethylpyrrolidine

8550 Example 1125B (341 mg, 1.00 mmol) was dissolved in 1 mL of piperidine and the mixture heated in a screw-cap vial to 100°C for 16 hours. The mixture was cooled to room temperature and concentrated. The residue was partitioned between water and 3 portions of ethyl acetate. The combined organic layers were washed with water, brine, dried filtered

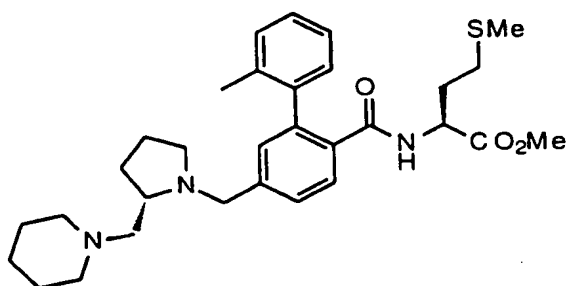
and concentrated to provide 234 mg (87%) of the title compound. (DCI, NH₃): 269 (MH⁺).



Example 1125C

2(S)-piperidin-1-ylmethylpyrrolidine, methyl ester

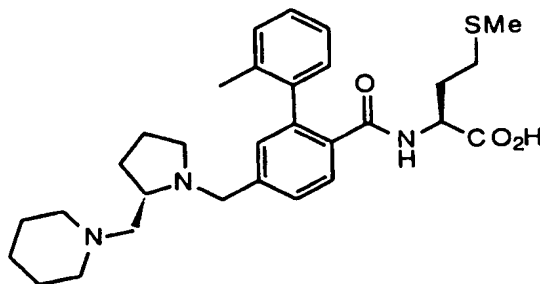
Using the procedure of example 1106C, example 1125C (230 mg, 0.85 mmol) provided 195 mg (100%) of the title compound. (DCI, NH₃): 159 (MH⁺).



Example 1125D

N-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Using the procedure described in example 1106D, part 1, example 1125C (195 mg, 0.86 mmol) provided 206 mg (77%) of the title compound. MS (ESI⁺): 538 (MH⁺); (ESI⁻): 536 (M-H).

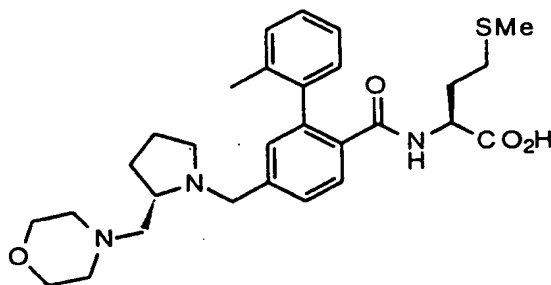


Example 1125E

N-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 1125D (195 mg, 0.36 mmol) provided 117 mg of the title compound. ¹H nmr (300 MHz., dmsO d6): δ 8.12, d, 1H;

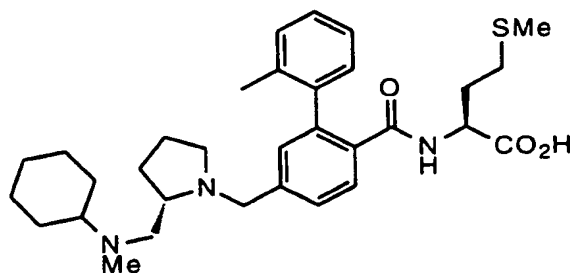
7.51, d, 1H; 7.43, d, 1H; 7.21, m, 2H; 7.14, m, 3H; 4.22, m, 2H; 3.55, d, 1H; 3.06, m, 1H; 2.90, m, 6H; 2.75, m, 1H; 2.41, m, 1H; 1.97 - 2.24, m, 6H; 1.96, s, 3H; 1.74, bm, 4H; 1.62, m, 4H; 1.45, m, 2H. MS (ESI+): 524 (MH+); (ESI-): 522 (M-H). Calc'd for $C_{30}H_{41}N_3O_3S \cdot 0.65 H_2O \cdot 1.00 TFA$; C 59.50; H 6.77; N 6.71; Found: C 60.10; H 6.89; N 6.46.



Example 1126

N-[4-(2-morpholin-4-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Prepared according to the procedure of example 1125 by substituting morpholine for piperidine in example 1125B. 1H nmr (300 MHz., dmso d6): δ 8.17, d, 1H; 7.53, d, 1H; 7.48, d, 1H; 7.28, m, 1H; 7.23, m, 2H; 7.15, m, 2H; 4.39, d, 1H; 4.23, m, 1H; envelope 3.00 - 3.90, 5H; 2.58, m, 1H; 2.51, m, 3H; 2.42, m, 4H; 1.97 - 2.24, m, 6H; 1.96, s, 3H; 1.79, bm, 3H; 1.62, m, 1H. MS (ESI+): 524 (MH+); (ESI-): 526 (M-H). Calc'd for $C_{29}H_{39}N_3O_4S \cdot 0.65 H_2O \cdot 0.55 TFA$; C 60.24; H 6.86; N 7.00; Found: C 60.26; H 6.94; N 6.87.

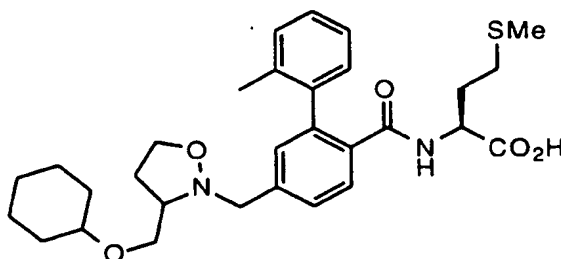


Example 1127

N-[4-(2-(N-cyclohexyl)-N-methylamino)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

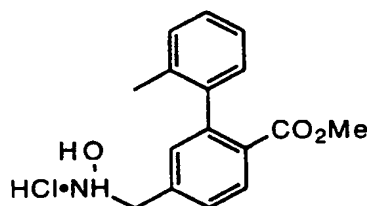
Prepared according to the procedure of example 1125 by substituting N-methylcyclohexylamine for piperidine in example 1125B. 1H nmr (300 MHz., dmso d6): δ

8.00, d, 1H; 7.49, d, 1H; 7.40, d, 1H; 7.20, m, 3H; 7.13, m, 2H; 4.22, m, 1H; 4.18, d, 1H; 3.47, d, 1H; envelope 2.60 - 2.95, 3H; 2.50, s, 3H; 2.42, s, 2H; 2.33, m, 1H; envelope 1.90 - 2.22, 6H; 1.96, s, 3H; 1.75, bm, 6H; 1.56, m, 2H; envelope 0.95 - 1.35, 6H. MS (ESI+): 552 (MH⁺); (ESI-): 550 (M-H). Calc'd for C₃₂H₄₅N₃O₃S•0.75 H₂O•0.50 TFA; C 63.69; H 7.61; N 6.75; Found: C 63.69; H 7.66; N 6.67.



Example 1130

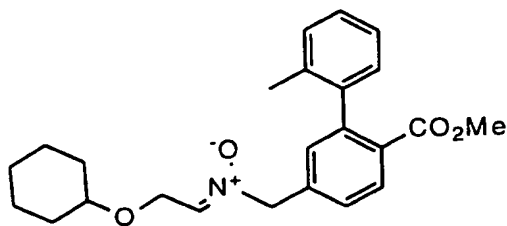
N-[4-(3-cyclohexyloxymethylisoxazolidin-2-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine



Example 1130A

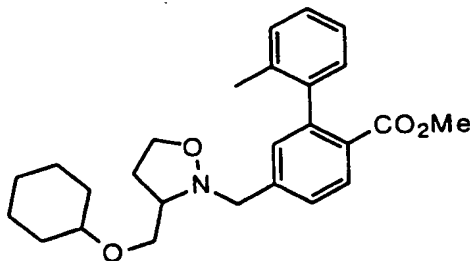
4-N-Hydroxyaminomethyl-2-(2-methylphenyl)benzoic acid, methyl ester

A solution of example 1178D (1.76 g (5.50 mmol) and N,O-bis-t-butoxycarbonylhydroxylamine (1.09 g, 5.00 mmol) in 10 mL of DMF were cooled in an ice bath and treated with sodium hydride (60%, 0.24 g, 6.00 mmol). After stirring for 4 hours, the mixture was quenched by the addition of pH 6 phosphate buffer and partitioned between water and 3 portion of ethyl ether. The combined organic fractions were washed with water and brine, dried, filtered and concentrated. The residue was dissolved in 10 mL of 4N HCl/dioxane and stirred overnight. The mixture was diluted with ethyl ether and placed in a freezer for 3 days. The precipitate was collected, washed with ether and dried under vacuum to provide 1.17 g (74%) of the title compound. MS (DCI, NH₃): 272 (MH⁺); 289 (M+NH₄)⁺.

Example 1130B

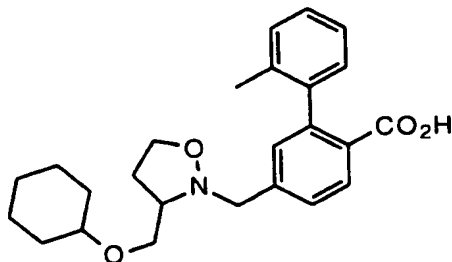
4-(N-Oxy-2-cyclohexyloxyacetaldoximinomethyl)-2-(2-methylphenyl)benzoic acid, methyl ester

A solution of example 1130A (1.15 g, 4.29 mmol) and 2-cyclohexyloxyacetaldehyde (0.55 g; 3.90 mmol) in 10 mL of acetonitrile was treated with powdered, activated 4Å molecular sieves (0.50 g) and potassium hydrogen carbonate (0.47 g, 4.70 mmol) and stirred overnight. The mixture was filtered through a plug of silica gel (prewetted with ether) and the pad washed well with ether. The filtrate was concentrated to provide 0.82 g (55%) of the title compound. MS (DCI, NH₃): 272 (MH)⁺.

Example 1130C

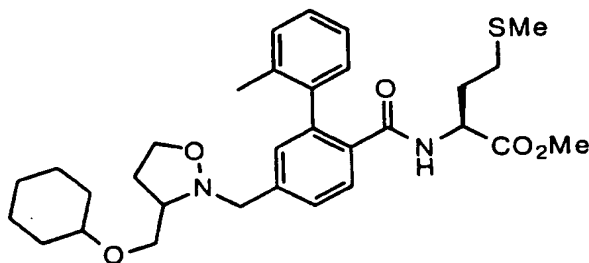
N-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoic acid methyl ester

A solution of example 1130B (0.81 g, 2.05 mmol) in 30 mL of chloroform was heated to 75°C under 640 psi of ethylene for 72 hours. The mixture was cooled to room temperature and vented. The chloroform was evaporated and the residue purified by column chromatography on silica gel (40 g, 15% ethyl acetate/hexanes) to provide 363 mg (40%) of the title compound. MS (ESI⁺): 424 (MH⁺).

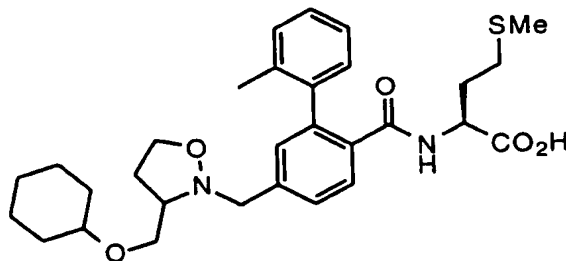


Example 1130D*N*-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoic acid

8655 A mixture of example 1130C (355 mg, 0.84 mmol) and sodium hydroxide (1 mL of a 4N aqueous solution, 4 mmol) in 4 mL of ethanol was heated to reflux for 6 hours and then cooled to room temperature. The mixture was diluted with water and the pH adjusted to 5 with aqueous phosphoric acid. The mixture was extracted with 3 portions of ethyl acetate and the combined organic fractions were washed with water and brine, dried, filtered and concentrated to provide 270 mg (78%) of the title compound. MS (ESI+): 410 (MH+).

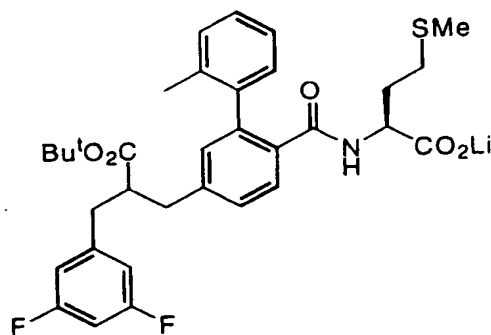
Example 1130E*N*-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

8665 Following the procedure of example 1178I, example 1130D (265 mg, 0.65 mmol) provided 147 mg (41%) of the title compound. MS (ESI+): 555 (MH+); (ESI-): 553 (M-H).

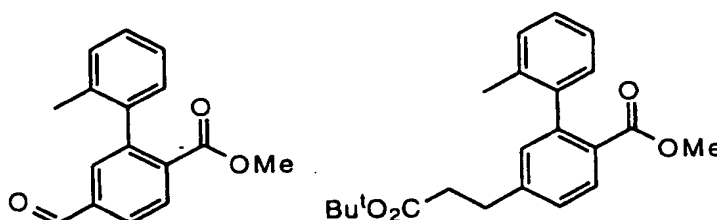
Example 1130F*N*-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8670 Following the procedure of example 1104, example 1130E (140 mg, 0.25 mmol) provided 78 mg (70%) after preparative HPLC purification. ¹H nmr (300 MHz., CDCl₃): δ 7.91, m, 1H; 7.56, m, 1H; 7.13 - 7.35, m, 5H; 5.99, d, 1H; 4.62, m, 2H; 4.41, m, 1H; 4.24, m, 1H; 4.05, m, 1H; 3.91, m, 1H; 3.52, m, 1H; 3.33, m, 1H; 2.40, m, 1H; 2.29, m, 1H; 2.00 - 2.28, m, 7H; 2.02, s, 3H; 1.89, bm, 3H; envelope, 1.43 - 1.75, 5H; 1.26, bm, 5H.

MS (ESI+): 541 (MH⁺): (ESI-): 539 (M-H). Calc'd for C₃₀H₄₀N₂O₅S•1.10 TFA; C 58.06; H 6.22; N 4.21; Found: C 57.97; H 6.28; N 4.17



Example 1135



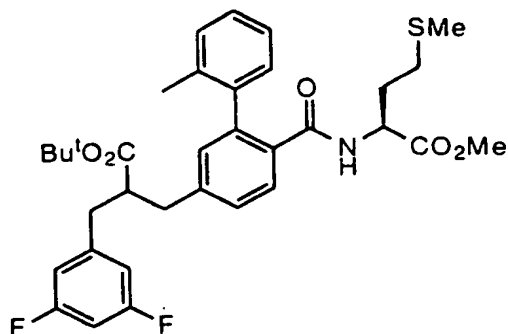
Example 1135A

Methyl 4-(tert-Butoxycarbonyl)ethyl-2-(2-methylphenyl)benzoate

To a solution of (t-butoxycarbonylmethyl)triphenylphosphonium bromide (10.98 g, 24.0 mmol) in THF (150 mL) at 0 °C was added potassium t-butoxide (1.0 M in THF, 24 mL) over 5 min. After 2 h, the aldehyde in THF (10 mL) was added slowly over 5 min., and the reaction was further stirred for 30 min. The reaction mixture was diluted with hexane (200 mL), and the resulting muddy mixture was filtered through silica gel (200 g), rinsed with ether, and concentrated to give an intermediate olefin. ¹H NMR (300 MHz, CDCl₃) δ 7.97 (d, 1 H), 7.59 (d, 1 H), 7.54 (dd, 1 H), 7.37 (d, 1 H), 7.30-7.27 (m, 3 H), 7.06 (d, 1 H), 6.44 (d, 1 H), 3.61 (s, 3 H), 2.06 (s, 3 H), 1.52 (s, 9 H). MS(Cl/NH₃) m/z: 353 (M+H)⁺, 370 (M+NH₄)⁺.

That intermediate was mixed with palladium on carbon (10%, 2.0 g) in ethanol (30 mL), and was stirred under a hydrogen balloon overnight. The mixture was then filtered through CeliteTM (5 g), and the filtrate was concentrated. The residue was then redissolved in ether (100 mL) and the solution was filtered through silica gel (30 g). Concentration of the filtrate afforded the title compound (7.27 g, 99% for 2 steps). ¹H NMR (300 MHz, CDCl₃)

8700 δ 7.91 (d, 1H), 7.28-7.15 (m, 4 H), 7.07-7.03 (m, 2 H), 3.60 (s, 3 H), 2.97 (t, 2 H), 2.57 (t, 2 H), 2.05 (s, 3 H), 1.40 (s, 9 H). MS(CI/NH₃) m/z: 355 (M+H)⁺, 372 (M+NH₄)⁺.



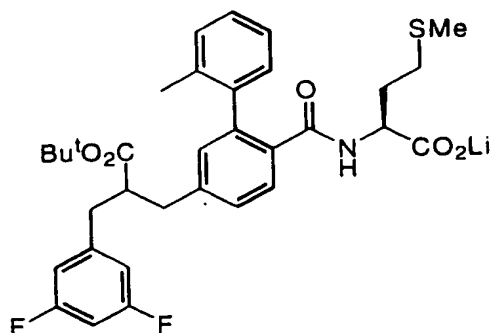
Example 1135B

8705 N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-methylphenyl)benzoyl]methionine Methyl Ester

To a -78 °C solution of intermediate 1135A (487 mg, 1.32 mmol) in THF (5 mL) was added sodium hexamethyldisilylazide (NaHMDS, 1.0 M in THF, 1.6 mL). After 30 min., 3,5-difluorobenzyl bromide (329 mg, 1.59 mmol) was added to the reaction, and the reaction mixture was then gradually warmed to room temperature over 2 h. The reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 8% ethyl acetate in hexane (the product and starting material had identical R_f on TLC) in to give the methyl ester intermediate.

8715 The product obtained from the previous step was stirred with saturated aqueous LiOH (2 mL) in MeOH (3 mL) at 50 °C overnight. Then, the reaction mixture was carefully adjusted to pH 3 to 4, and extracted with ethyl acetate (100 mL). The organic layer was rinsed once with brine (15 mL), and dried with anhydrous magnesium sulfate, filtered, and concentrated. The crude monoacid obtained this way was stirred with L-methionine methyl ester hydrochloride (383 mg, 2 mmol), 1-hydroxybenzotriazole (266 mg, 2.0 mmol), triethylamine (303 mg, 3.0 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (400 mg, 2.0 mmol) in DMF for 5 h. The reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with water (2 X 20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 20% ethyl acetate in hexane to give the title compound (277 mg, 34% for 3 steps). ¹H NMR (300 MHz, CDCl₃) δ 7.92 (2 d's, 1 H), 7.37-7.12 (m, 5 H), 7.02 (d, 1 H), 6.75-6.60 (m, 3 H), 5.90 (br d, 1 H), 4.62 (m, 1

8730 H), 3.66 (s, 3H), 3.05-2.72 (m, 5 H), 2.17,2.06,2.02,2.00 (4 s's, 6 H), 2.03 (m, 2 H), 1.95 (m, 1 H), 1.60 (m, 1 H), 1.22 (3 s's, 9 H). MS(CI/NH₃) m/z: 612 (M+H)⁺.

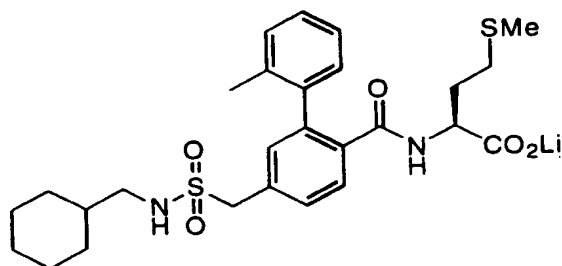


Example 1135C

8735 N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

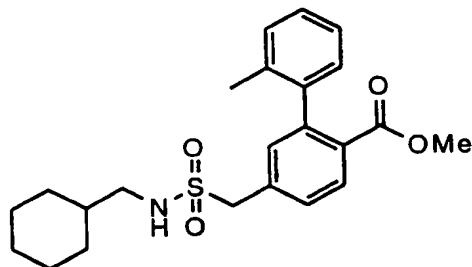
The procedure described in the Example 403I was used here to convert the intermediate 1135B (66 mg) to the title lithium salt (65 mg, 100%). ¹H NMR (300 MHz, MeOD-d₄) δ 7.52 (br s, 1 H), 7.35-7.21 (m, 5 H), 7.06 (m, 1 H), 6.87-6.72 (m, 3 H), 4.24 (m, 1 H), 3.00-2.85 (m, 5 H), 2.08-1.93 (m, 8 H), 1.84 (m, 1 H), 1.65 (m, 1 H), 1.18-1.12 (3 s's, 9 H). MS(ESI⁻) m/z: 596 (M-H)⁻.

8740



Example 1138

8745



Example 1138A

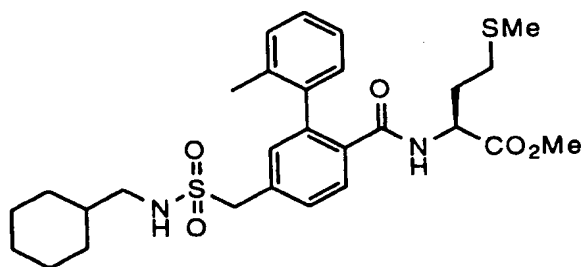
Methyl 4-(N-Cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoate

8750 To a room temperature solution of 1178D (1.21 g, 3.79 mmol) in THF (10 mL) was added potassium thioacetate (0.48 g, 4.2 mmol). After 5 hours, NaOH (3.5 M in water, 3 mL) was added, and the reaction mixture was stirred another 30 min. Reaction mixture was then acidified with HCl (1.0 M, 15 mL), and partitioned between ethyl acetate (100 mL) and water (10 mL). The organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated.

8755 The residue desolved acetic acid (5 mL) and hydrogen peroxide (30%, 5 mL), and heated at 80 °C for 16 hours. The reaction mixture was diluted with brine (10 mL), and extrated with ethyl acetate (3 X 30 mL). The combined extrats were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to give the crude sulfonic acid. MS(ESI-) m/z: 319 (M-H)⁻.

8760 The crude sulfonic acid was then refluxed with thionyl chloride (5 mL) and DMF (0.5 mL) for 8 hours. Solvent was then evaporated, and the residue was dried under high vacuum (5 mmHg) for 3 hours. The sulfonyl chloride obtained this way was then desolved in DCM (10 mL), and to it was added cyclohexylmethylamine (0.5 g) and triethylamine (2 mL). Afte 20 min., the reaction was diluted with ether (20 mL), filtered through silica gel (20 g), rinsed with ether (50 mL), and concentrated. The residue was purified by column chromatography with hexane:chloroform:ethyl acetate (50:50:10) to give the title compound (61 mg, 3.9%, 3 steps). 7.97 (d, 1 H), 7.46 (dd, 1 H), 7.30-7.15 (m, 5 H), 7.05 (br d, 1 H), 4.30 (s, 2 H), 3.61 (s, 3 H), 2.83 (t, 2 H), 2.07 (s, 3 H), 1.80-0.90 (m, 11 H).MS(Cl/NH₃) m/z: 433 (M+NH₄)⁺.

8770



Example 1138B

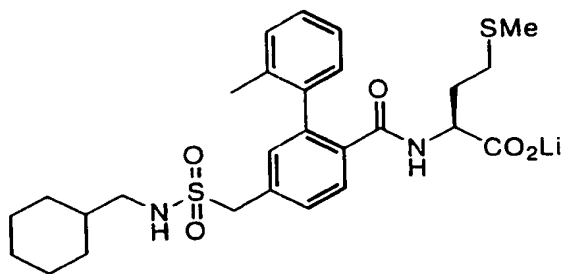
N-[4-(N-Cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8775

Methyl Ester

The procedures described in the Example 403E and 403F were used here to convert the above intermediate 1138A (45 mg) to the title methyl ester (37 mg, 63%). ¹HNMR (300 MHz, CDCl₃) δ 7.97 (2 d'd, 1 H), 7.48 (d, 1 H), 7.37-7.22 (m, 5 H), 5.93 (d, 1 H), 4.63

(m, 1 H), 4.29 (s, 2 H), 3.67 (s, 3 H), 2.87 (t, 2 H), 2.20-2.00 (m, 8 H), 2.86 (m, 1 H),
 8780 2.80-0.80 (m, 12 H). MS(ESI-) m/z: 545 (M-H)⁻.



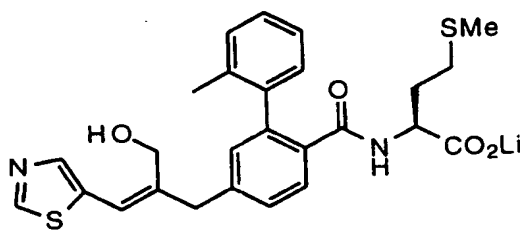
Example 1138C

N-[4-(N-Cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Lithium Salt

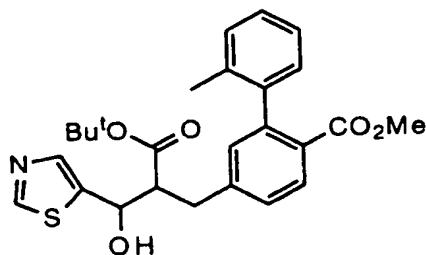
8785 The procedure described in the Example 403I was used here to convert the intermediate 1135B (32 mg) to the title lithium salt (32 mg, 100%). ¹H NMR (300 MHz, dmso-d₆) δ 7.46 (d, 1 H), 7.36 (m, 1 H), 7.20-6.92 (m, 6 H), 7.08 (m, 1 H), 4.30 (s, 2 H), 3.58 (m, 1 H), 2.64 (br d, 2 H), 2.00-1.80 (m, 8 H), 1.80-0.68 (m, 13 H). MS(ESI-) m/z: 531 (M-H)⁻.

8790



Example 1162

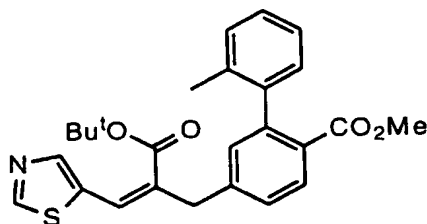
8795



Example 1162A

Methyl 4-[2-*t*-Butoxycarbonyl-3-hydroxy-3-(thiazol-5-yl)propyl]-2-(2-methylphenyl)benzoate

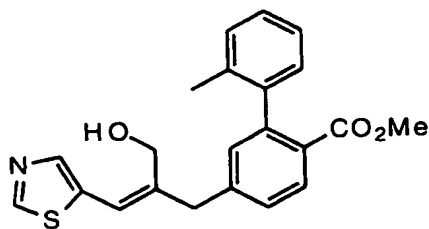
8800 To a -78 °C solution of intermediate 1135A (1.75 g, 4.94 mmol) in THF (20 mL) was added sodium hexamethyldisilylazide (1.0 M in THF, 5.9 mL). After 10 min, 5-thiazolcarboxaldehyde (838 mg, 7.41 mmol) in THF (10 mL) was added to the reaction, and the reaction mixture was then gradually warmed to room temperature over 2 h. The reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL).
 8805 The organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 50% ethyl acetate in hexane to give the title intermediate as a mixture of diastereomers (1.41 g, 61%, ratio of diastereomers, 2.5:1). ¹H NMR (300 MHz, CDCl₃) δ 8.90 (2 br s's, 1 H), 7.91 (2 d's, 1 H), 7.80 (2 br s's, 1 H), 7.31-7.25 (m, 5 H),
 8810 7.05 (m, 2 H), 5.30, 5.05 (2 m's, 1 H), 3.60 (s, 3 H), 3.14-3.00 (m, 3 H), 2.05 (4 s's, 3 H), 1.26, 1.19, 1.18 (3 s's, 9 H). MS(Cl/NH₃) m/z: 468 (M+H)⁺.



Example 1162B

8815 Methyl 4-[E-2-*t*-Butoxycarbonyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoate

To a solution of intermediate 1162A (267 mg, 0.57 mmol) in 1,2-dichloroethane (10 mL) was added pyridine (0.5 mL), POCl₃ (0.2 mL) and DBU (5 drops) in that order. After 4 hours at room temperature, the reaction mixture was diluted with ether (10 mL), filtered through silica gel (30 g), rinsed with ether (2 X 20 mL), and concentrated. The residue
 8820 was purified by column chromatography with 30% ethyl acetate in hexane to give the title compound as a single isomer (230 mg, 90%). ¹H NMR (300 MHz, CDCl₃) δ 8.81 (s, 1 H), 8.02 (s, 1 H), 7.96 (s, 1 H), 7.89 (d, 1 H), 7.26-7.15 (m, 5 H), 7.02 (m, 2 H), 4.06 (br s, 2 H), 3.59 (s, 3 H), 2.00 (s, 3 H), 1.43 (s, 9 H). MS(Cl/NH₃) m/z: 450 (M+H)⁺.

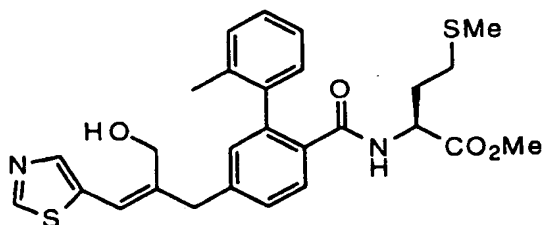


Example 1162C

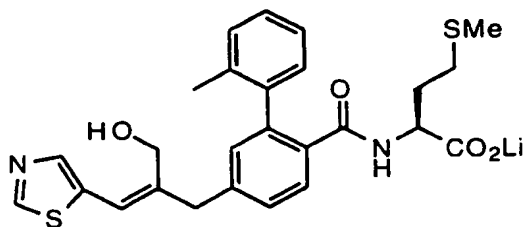
8825

Methyl 4-[E-2-Hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoate

A mixture of intermediate 1162B (205 mg, 0.456 mmol) and HCl (anhydrous, 4.0 M in 1,4-dioxane, 2 mL) was stirred for 16 h at room temperature. The reaction mixture was then concentrated to dryness, and the residue was desolved in THF (3 mL) and cooled to 0 °C. To it was added isobutyl chloroformate (0.089 mL, 0.685 mmol) and *N*-methylmorpholine (0.15 mL, 1.4 mmol). After 15 min. at 0 °C, sodium borohydride (53 mg, 1.4 mmol) was added to the reaction, followed by addition of methanol (1 mL). The reaction was then stirred at room temperature for 2 hours. The reaction mixture was then partitioned between ethyl acetate (50 mL) and water (5 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 50% ethyl acetate in hexane to give the title compound (69.7 mg, 40%). ¹H NMR (300 MHz, CDCl₃) δ 8.70 (s, 1 H), 7.90 (d, 1 H), 7.81 (s, 1 H), 7.27-7.15 (m, 4 H), 7.05 (m, 2 H), 6.93 (s, 1 H), 4.21 (d, 2 H), 3.85 (s, 2 H), 3.59 (s, 3 H), 2.02 (s, 3 H). MS(CI/NH₃) *m/z*: 380 (M+H)⁺.

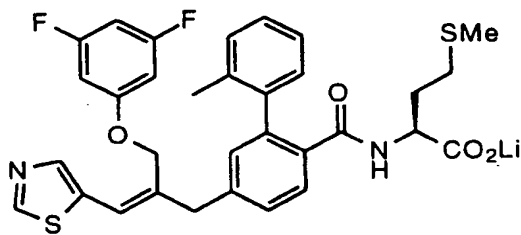
Example 1162 D*N*-(4-[E-2-Hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl)methionine Methyl Ester

The procedures described in the Example 403E and 403F were used here to convert the intermediate 1162D (69 mg) to the title methyl ester (74 mg, 80%). ¹H NMR (300 MHz, CDCl₃) δ 8.78 (s, 1 H), 7.95-7.81 (m, 2 H), 7.35-7.15 (m, 5 H), 7.01 (s, 1 H), 6.94 (s, 1 H), 5.86 (m, 1 H), 4.62 (m, 1 H), 4.22 (s, 2 H), 3.84 (s, 2 H), 3.77 (s, 3 H), 2.14-2.00 (m, 8 H), 1.87 (m, 1 H), 1.60 (m, 1 H). MS(CI/NH₃) *m/z*: 511 (M+H)⁺.

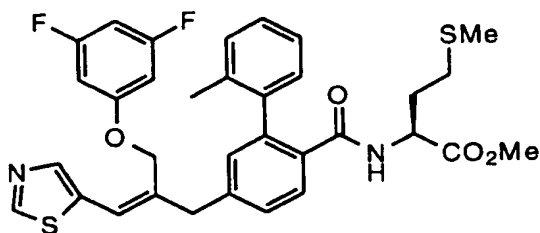
Example 1162 E

N-(4-[*E*-2-Hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl)methionine Lithium Salt

The procedure described in the Example 403I was used here to convert the intermediate 1162D (20.2 mg) to the title lithium salt (20 mg, 100%). ¹H NMR (300 MHz, dmso-d₆) δ 8.97 (s, 1 H), 7.90 (s, 1 H), 7.47 (d, 1 H), 7.25 (dd, 1 H), 7.22-7.07 (m, 4 H), 6.92 (m, 2 H), 6.89 (m, 1 H), 5.42 (t, 1 H), 3.99 (d, 2 H), 3.75 (s, 2 H), 3.60 (m, 1 H), 2.08 (m, 1 H), 1.95 (m, 1 H), 1.90 (br s, 6 H), 1.68 (m, 1 H), 1.55 (m, 1 H). MS(ESI-) m/z: 495 (M-H)⁻:



Example 1163

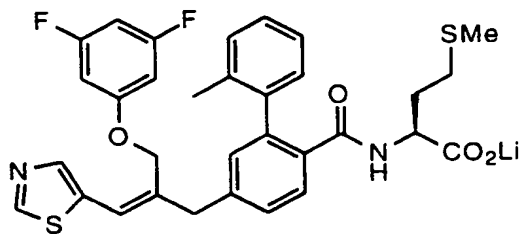


Example 1163A

N-(4-[*E*-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl)methionine Lithium Salt

To a 0 °C solution of triphenylphosphine (55 mg, 0.21 mmol) in DCM (1 mL) was added diethyl azodicarboxylate (36 mg, 0.21 mmol). After 10 min., the solution thus prepared was transferred to a 0 °C solution of intermediate 1162D (35.1 mg, 0.069 mmol) and 3,5-difluorophenol (27.3 mg, 0.21 mmol) in DCM (1 mL). After the reaction mixture was stirred at room temperature for 15 hours, it was diluted with ether (5 mL), filtered through silica gel (5 g), rinsed with ether (10 mL), and concentrated. The residue was purified twice by column chromatography with 30% ethyl acetate in hexane to give the title methyl ester (13.2 mg, 31%). ¹H NMR (300 MHz, CDCl₃) δ 8.78 (s, 1 H), 7.95-7.85 (m, 2 H), 7.35-7.05 (m, 9 H), 7.02 (s, 1 H), 6.97 (s, 1 H), 5.88 (m, 1 H), 4.62 (m, 1 H),

4.49 (s, 2 H), 3.92 (s, 2 H), 3.66 (s, 3 H), 2.17-1.98 (m, 8 H), 1.87 (m, 1 H), 1.60 (m, 1 H). MS(CI/NH₃) m/z: 623 (M+H)⁺.



8885

Example 1163B

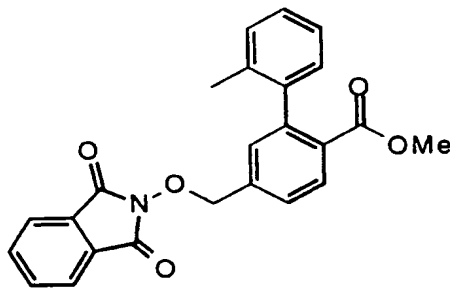
N-[4-[E-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

The procedure described in the Example 403I was used here to convert the intermediate 1163A (13.2 mg) to the title lithium salt (13.0 mg, 100%). ¹H NMR (300 MHz, dms_o-d₆) δ 9.05 (s, 1 H), 7.98 (s, 1 H), 7.47 (d, 1 H), 7.25 (dd, 1 H), 7.22-7.07 (m, 5 H), 6.95 (m, 1 H), 6.87 (m, 1 H), 6.80-6.70 (m, 4 H), 4.62 (s, 2 H), 3.87 (s, 2 H), 3.60 (m, 1 H), 2.10-1.92 (m, 2 H), 1.90 (br s, 6 H), 1.68 (m, 1 H), 1.55 (m, 1 H). MS(ESI⁻) m/z: 607 (M-H)⁻.

8895

Example 1176

8900



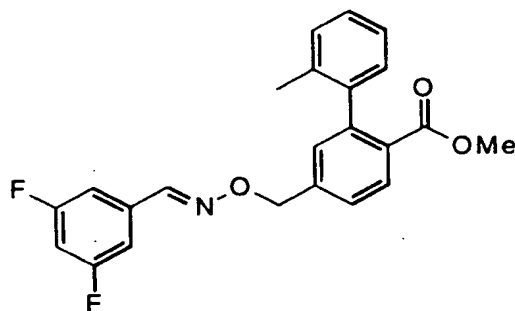
Example 1176A

4-Phthalimidoyloxymethyl-2-(2-methylphenyl)benzoic acid methyl ester

To a stirred solution at 0°C under N₂ of 4-hydroxymethyl-2-(2-methylphenyl)benzoic acid methyl ester (5.00 g, 19.5 mmol), prepared as in Example 1178A-C, N-hydroxyphthalimide (3.19 g, 19.5 mmol), and triphenylphosphine (5.12 g,

8905

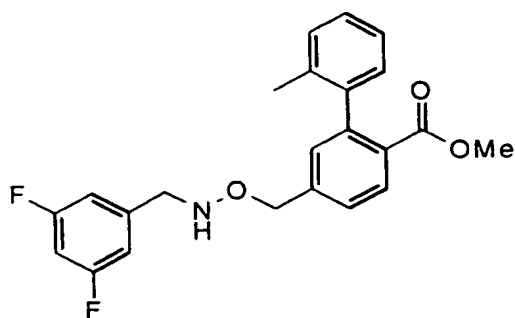
19.5 mmol) in anhydrous THF (150 mL) was added diethyl azodicarboxylate (3.38 mL, 21.5 mmol). Cooling bath removed and reaction warmed to 50°C overnight. Solvents concentrated *in vacuo*, and residue taken up in ether and washed with 2M Na₂CO₃ (3x), water, and brine. Organic layer dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Residue was purified by flash chromatography on silica gel eluting with 20% EtOAc/Hexanes to afford the desired product as a white solid (3.32 g, 41%). ¹H (300MHz, CDCl₃, δ) 7.99 (1H, d, J=8Hz), 7.79 (4H, m), 7.63 (1H, dd, J=7&2Hz), 7.38 (1H, d, J=2Hz), 7.30-7.10 (3H, m), 7.02 (1H, dd, J=8&2Hz), 5.26 (2H, s), 3.62 (3H, s), 1.99 (3H, s).



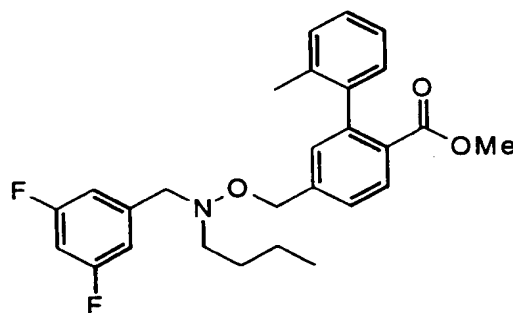
Example 1176B

4-(N-(3,5-difluorobenzylidenenyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester

To a solution under N₂ of 4-phthalimidoyloxymethyl-2-(2-methylphenyl)benzoic acid methyl ester (575 mg, 1.43 mmol), prepared as in Example 1176A, in boiling EtOH (10 mL) was added while hot 55% hydrazine hydrate (0.089 mL, 1.58 mmol). Reaction allowed to cool to ambient temperature, and to this mixture was added 3,5-difluorobenzaldehyde (0.172 mL, 1.58 mmol). Reaction stirred overnight at ambient temperature. Solvents concentrated *in vacuo*, and residue stirred with CCl₄ (30 mL) and MgSO₄ for 15 minutes at ambient temperature. Mixture filtered through celite, and filtrate concentrated *in vacuo*. Residue was purified by flash chromatography on silica gel eluting with 10% EtOAc/Hexanes to afford the desired product as a pale yellow solid (551 mg, 97%). m/e (ESI) 396 (MH⁺)

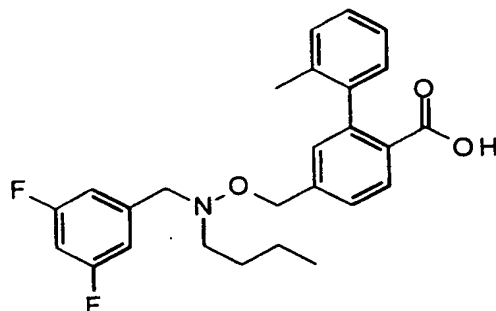
Example 1176C4-(N-(3,5-difluorobenzyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester

8935 To a stirred solution at room temperature under N₂ of 4-(N-(3,5-
 difluorobenzylidenoyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester (551
 mg, 1.40 mmol), prepared as in Example 1176B, in MeOH (5 mL) was added sodium
 cyanoborohydride (263 mg, 4.18 mmol) and bromocresol green indicator. To this was
 added a 1:1 solution of conc. HCl/MeOH dropwise to maintain a yellow-orange color (pH
 8940 less than 3). After reaction mixture remained yellow, it was allowed to stir 30 minutes at
 room temperature. Reaction quenched with 1.0M NaHCO₃, and product extracted out with
 EtOAc (2x). Extracts washed with 1.0M NaHCO₃ (2x) and brine, dried with Na₂SO₄,
 filtered, and concentrated *in vacuo*. Residue was purified by flash chromatography on silica
 gel eluting with 25% EtOAc/Hexanes to afford the desired product. (254 mg, 46%). m/e
 8945 (ESI) 398 (MH⁺)

Example 1176D4-(N-Butyl-N-(3,5-difluorobenzyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester

8950 To a stirred solution at ambient temperature under N₂ of 4-(N-(3,5-
 difluorobenzyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester (254 mg,
 0.640 mmol), prepared as in Example 1176 C, in DMF (2 mL) was added potassium
 carbonate (265 mg, 1.92 mmol) and 1-iodobutane (0.146 mL, 1.28 mmol). Reaction stirred

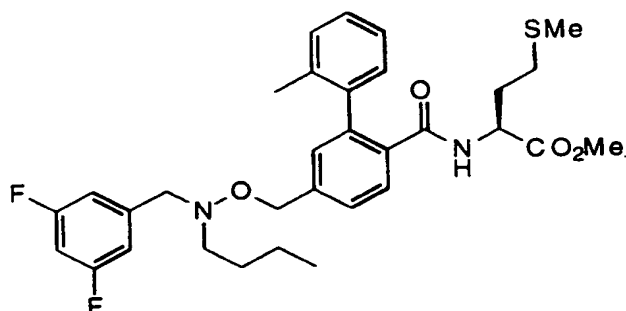
8955 vigorously at 80°C overnight. Reaction diluted with EtOAc and washed with water and brine. Organic layer dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Residue was purified by flash chromatography on silica gel eluting with 7% EtOAc/Hexanes to 30% EtOAc/Hexanes to afford the desired product. (44 mg, 15%). m/e (ESI) 454 (MH⁺)



8960 Example 1176E

4-(N-Butyl-N-(3,5-difluorobenzyl)aminoxyethyl)-2-(2-methylphenyl)benzoic acid

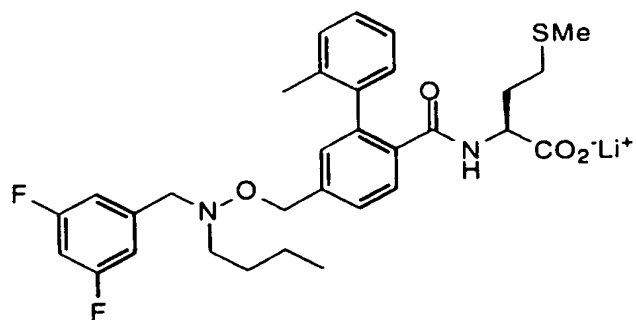
The desired acid was prepared using the method described in Example 403E starting with the compound prepared in Example 1176D.



8965 Example 1176F

N-[4-N-Butyl-N-(3,5-difluorobenzyl)aminoxyethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

8970 The desired product was prepared using the method described in Example 403F starting with the compound prepared in Example 1176E.

Example 1176G

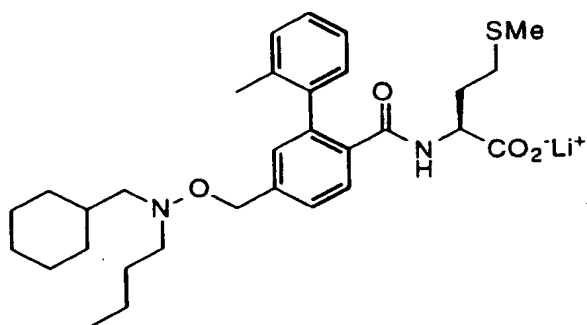
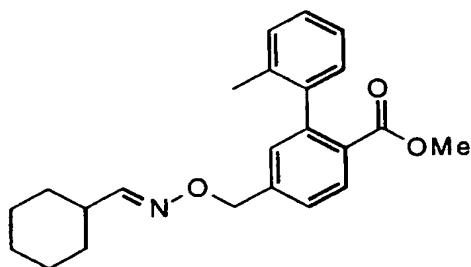
8975

N-[4-*N*--Butyl-*N*-(3,5-difluorobenzyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

8980

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1176F. ¹H (300MHz, CDCl₃, δ) 7.70 (1H, m), 7.30-7.00 (6H, m), 6.94 (1H, m), 6.85 (1H, dd, J=7&2Hz), 6.65 (1H, m), 4.53 (2H, bs), 4.03 (1H, m), 3.80 (2H, bs), 2.72 (2H, t, J=8Hz), 2.30-1.90 (5H, m), 1.80 (3H, s), 1.58 (2H, m), 1.50-1.20 (4H, m), 0.87 (3H, t, J=8Hz). m/e (ESI) 569 (MH⁺)

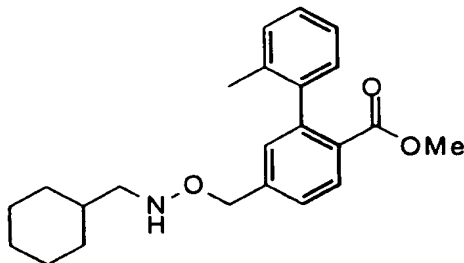
8985

Example 1186Example 1186A

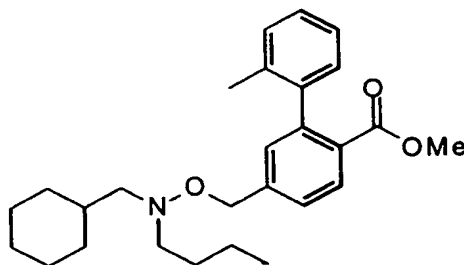
8990

4-N-(Cyclohexylmethylidene)aminooxymethyl-2-(2-methylphenyl)benzoic acid methyl ester

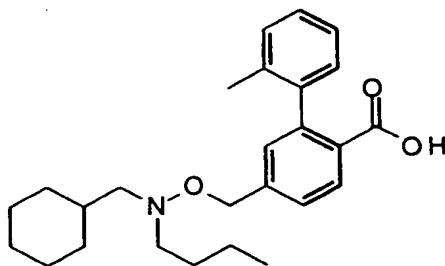
The desired product was prepared using the method described in Example 1176B starting with 4-phthalimidoyloxymethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in Example 1176A and cyclohexanecarboxaldehyde. m/e (ESI) 366 (MH⁺)

Example 1186B4-N-(Cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoic acid methyl ester

The desired product was prepared using the method described in Example 1176C starting with the compound in Example 1186A. m/e (ESI) 368 (MH⁺)

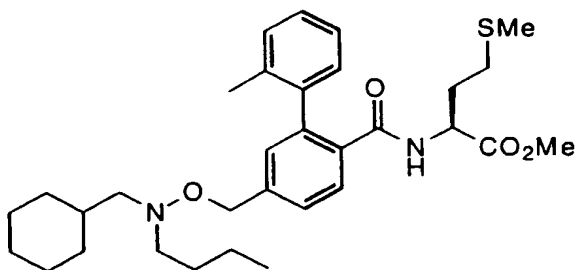
Example 1186CN-[4-N-Butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoic acid methyl ester]

The desired product was prepared using the method described in Example 1176D starting with the compound in Example 1186B. m/e (ESI) 424 (MH⁺)

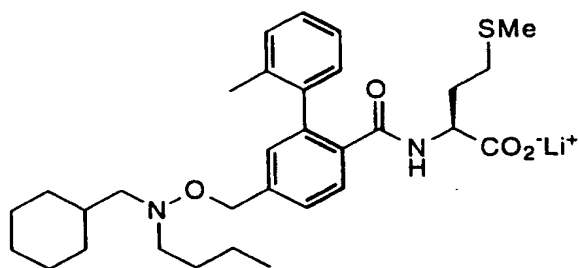
Example 1186D

N-[4-*N*--Butyl-*N*-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoic acid

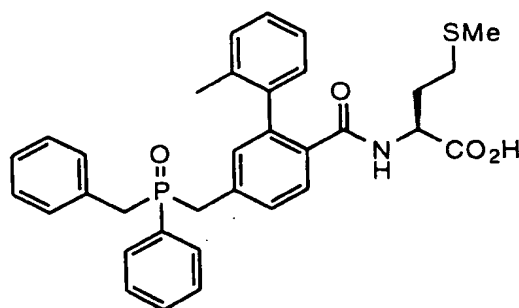
The desired product was prepared using the method described in Example 403E starting with the compound in Example 1186C.

Example 1186E*N*-[4-*N*--Butyl-*N*-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired product was prepared using the method described in Example 403F starting with the compound in Example 1186D. *m/e* (ESI) 555 (MH⁺)

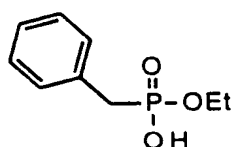
Example 1186F*N*-[4-*N*--Butyl-*N*-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 403I starting with the compound in Example 1186E. ¹H (300MHz, DMSO-d₆, δ) 7.53 (1H, d, J=9Hz), 7.37 (1H, dd, J=7&2Hz), 7.30-7.05 (5H, m), 6.96 (1H, m), 4.63 (2H, s), 3.68 (1H, m), 2.62 (2H, t, J=8Hz), 2.42 (2H, d, J=8Hz), 2.25-1.95 (5H, m), 1.92 (3H, s), 1.80-1.50 (7H, m), 1.42 (3H, m), 1.26 (2H, m), 1.13 (3H, m), 0.85 (5H, t, J=8Hz). *m/e* (ESI) 539 (MH⁻) Anal.calc. for C₃₁H₄₃LiN₂O₄S·0.75 H₂O C 66.46, H 8.01, N 5.00 Found C 66.43, H 8.02, N 4.88



9035 Example 1211

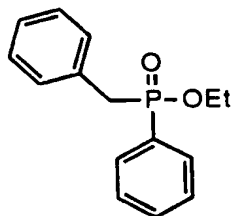
N-[4-(Benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine



9040 Example 1211A

Benzylphosphonic acid monoethyl ester

Diethyl benzylphosphonate (5.0 mL, 5.5 g, 24 mmol) was dissolved in absolute EtOH (25 mL), then 50% NaOH (3 mL) was added. The reaction was heated under reflux overnight, allowed to cool to RT, then partitioned between 2N HCl and EtOAc. Washed organic layer with brine, extracted combined aqueous layers with EtOAc, dried combined organic layers over Na₂SO₄. After filtration and concentration recovered 4.5 g (93%). MS (DCI/NH₃) 201/218 (M+H)⁺/ (M+H+NH₃)⁺.

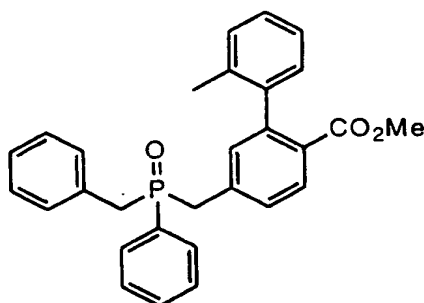


9050 Example 1211B

Benzylphenylphosphinic acid ethyl ester

The compound described in Example 1211A (2.5 g, 12.5 mmol) was dissolved in CH₂Cl₂ (100 mL), cooled to 0-5 °C, then added DMF (50 μL) and oxalyl chloride (1.25 mL, 1.82 g, 14.3 mmol). After 15 min. removed the bath, and let the reaction warm to RT over 1 h. The reaction was then concentrated, dissolved in toluene, reconstituted, dissolved in Et₂O (8 mL), and cooled to -10 °C. Under N₂, 3.0M phenylmagnesium chloride (3.3 mL) was added dropwise (removed bath after ca. 7 mL had been added

because the reaction was too thick to stir). Stirred the reaction at RT for 3 h, then partitioned between 2N HCl and Et₂O. Washed organic layer with water and brine, then dried over Na₂SO₄. After filtration and concentration the compound was purified by chromatography using 1/4 hex/ EtOAc. Recovered 1.38 g (42%). MS (DCI/NH₃) 261/278 (M+H)⁺/ (M+H+NH₃)⁺.

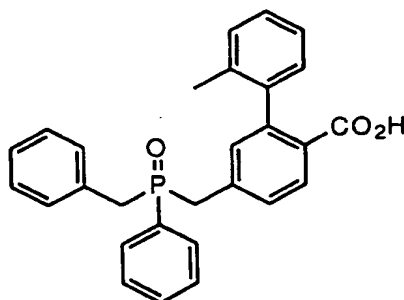


Example 1211C

4-(Benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

The title compound was prepared from the compound described in Example 1211B and the bromide described in Example 1178D using the method found in JACS, 94, 1774 (1972).

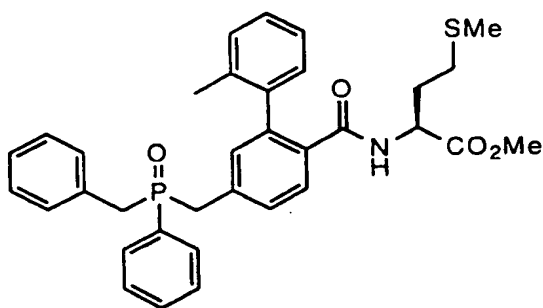
After chromatography using 1/2 hex/EtOAc the product still contained 35-40% (wt.) starting ethyl phosphinate. MS (APCI) 455 (M+H)⁺ & 261 (M+H)⁺ (for starting material).



Example 1211D

4-(Benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

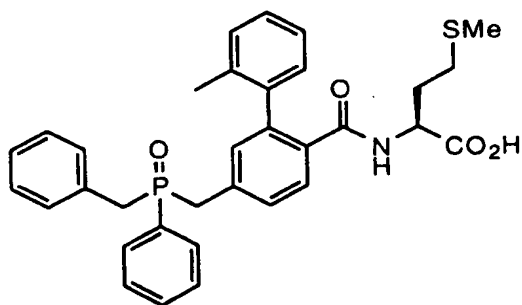
The title compound was prepared from the compound described in Example 1211C by the method of Example 1178H. The title compound was separated from the phosphinic acid by chromatography using 98/2/0.5 CHCl₃/ MeOH/ CH₃CO₂H. MS (ESI) 439 (M-H)⁻.



Example 1211E

N-[4-(Benzyldiphenyl(oxophosphiny)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

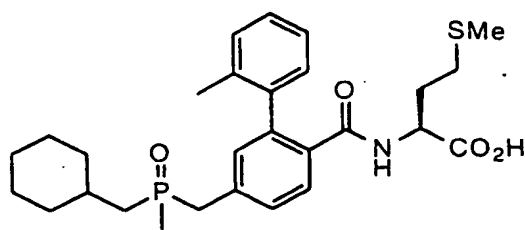
The title compound was prepared from the compound described in Example 1211D using the method of Example 1205D, except the chromatography used 1.5% EtOH in EtOAc. MS (APCI) 586 (M+H)⁺.



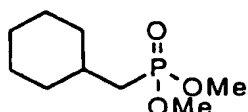
Example 1211F

N-[4-(Benzyldiphenyl(oxophosphiny)methyl)-2-(2-methylphenyl)benzoyl]methionine

The above compound was prepared from the compound described in Example 1211E according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.08 (m, 1H), 7.68 (m, 2H), 7.45 (m, 4H), 7.36 (d, 1H), 7.17, 7.10, 6.92, 6.82 (all m, total 10H), 4.19 (m, 1H), 3.50 (m, 4H), 2.10, 1.95, 1.80 (all m, total 10H). MS (ESI) 570 (M-H)⁻. Anal calcd for C₃₃H₃₄NO₄PS·0.15 CHCl₃: C, 67.53; H, 5.84; N, 2.38. Found: C, 67.55; H, 5.90; N, 2.24.

Example 1212

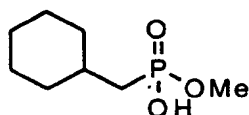
N-[4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

Example 1212A

Cyclohexylmethylphosphonic acid dimethyl ester

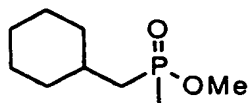
Using the Grignard reagent made from bromomethyl cyclohexane and dimethyl phosphochloridate, the title compound was prepared by the method found in Engel, Robert, ed. Synthesis of Carbon-Phosphorous Bonds, p. 179. Boca Raton, FL: CRC Press, 1988.

The compound was purified by chromatography using EtOAc. MS (DCI/NH₃) 207/224 (M+H)⁺/ (M+H+NH₃)⁺.

Example 1212B

Cyclohexylmethylphosphonic acid monomethyl ester

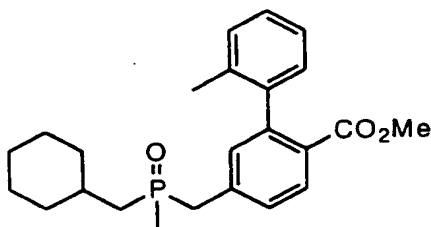
The title compound was prepared from the compound described in Example 1212A by the method of Example 1211A. MS (DCI/NH₃) 193/210 (M+H)⁺/ (M+H+NH₃)⁺.

Example 1212C

(Cyclohexylmethyl)methylphosphonic acid methyl ester

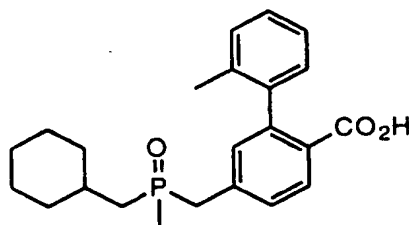
The title compound was prepared from the compound described in Example 1212B and methylmagnesium bromide by the method of Example 1211B. MS (DCI/NH₃) 191/208 (M+H)⁺/ (M+H+NH₃)⁺.

9125

Example 1212D4-(((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

9130

The title compound was prepared from the compound described in Example 1212C and the bromide described in Example 1178D using the method found in JACS, **94**, 1774 (1972), followed by purification with chromatography using EtOAc/EtOH 93/7. MS (DCI/NH₃) 399/416 (M+H)⁺/ (M+H+NH₃)⁺.

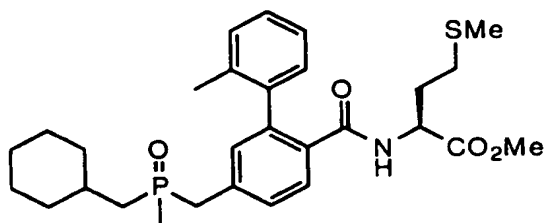


9135

Example 1212E4-(((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

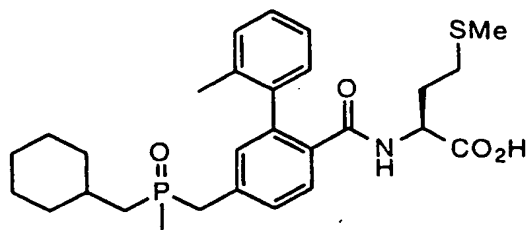
The title compound was prepared from the compound described in Example 1212D using the method of Example 1178H. MS (DCI/NH₃) 385/402 (M+H)⁺/ (M+H+NH₃)⁺.

9140

Example 1212FN-[4-(((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

9145

The above compound was prepared from the compound described in Example 1212E according to the method of Example 1205D. MS (APCI) 530 (M+H)⁺.

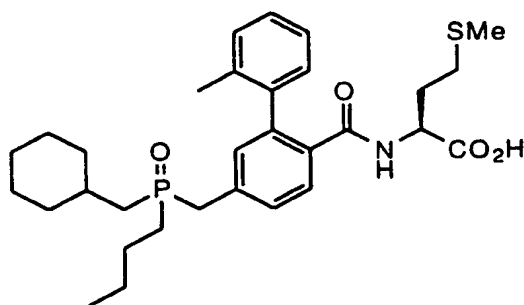
Example 1212G

9150

N-[4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-
methylphenyl)benzoyl]methionine

The above compound was prepared from the compound described in Example 1212F according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.08 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (dd, 2H), 2.10 (m, 5H), 1.95 (s, 3H), 1.80, 1.60 (both m, total 10H), 1.30 (d, 3H), 1.20, 1.00 (both m, total 5H). MS (ESI) 514 (M-H)⁻. Anal calcd for C₂₈H₃₈NO₄PS: C, 65.22; H, 7.43; N, 2.72. Found: C, 64.86; H, 7.44; N, 2.60.

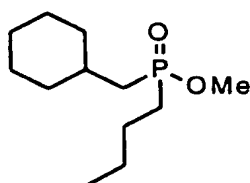
9155



9160

Example 1213

N-[4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-
methylphenyl)benzoyl]methionine

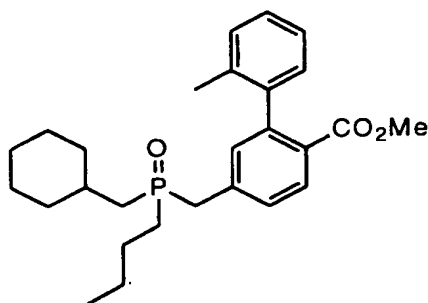


9165

Example 1213A

(Cyclohexylmethyl)butylphosphinic acid methyl ester

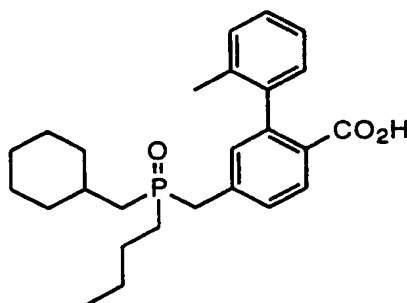
The title compound was prepared from the compound described in Example 1212B and butylmagnesium chloride by the method of Example 1211B. MS (DCI/NH₃) 233/250 (M+H)⁺/ (M+H+NH₃)⁺.



Example 1213B

4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

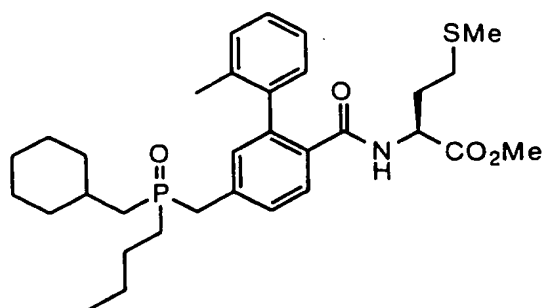
The title compound was prepared from the compound described in Example 1213A and the bromide described in Example 1178D using the method of Example 1212D. MS (DCI/NH₃) 441/458 (M+H)⁺/ (M+H+NH₃)⁺.



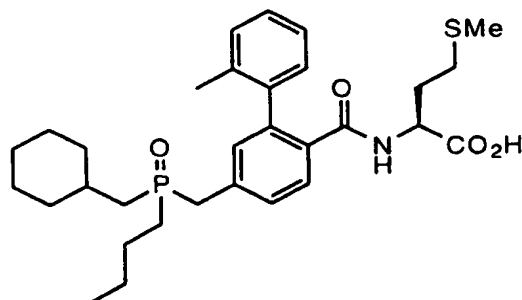
Example 1213C

4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1213B using the method of Example 1178H. MS (DCI/NH₃) 427/444 (M+H)⁺/ (M+H+NH₃)⁺.

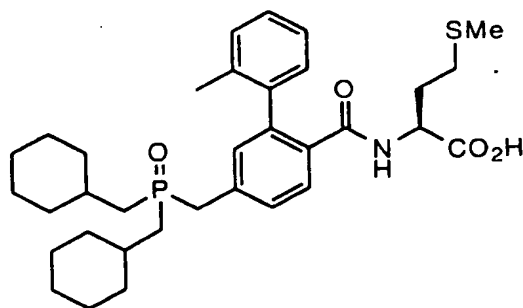
**Example 1213D****N-[4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester**

9190 The above compound was prepared from the compound described in Example 1213C according to the method of Example 1205D. MS (APCI) 572 (M+H)⁺.

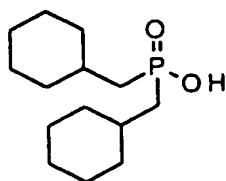
**Example 1213E****N-[4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine**

9195 The above compound was prepared from the compound described in Example 1213D according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.08 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.85-0.90 (envelope 21H), 0.85 (t, 3H). MS (ESI) 556 (M-H)⁻. Anal calcd for C₃₁H₄₄NO₄PS: C, 66.76; H, 7.95; N, 2.51. Found: C, 66.73; H, 8.00; N, 2.42.

9200



9205

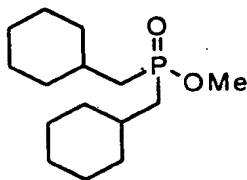
Example 1214N-[4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

9210

Example 1214ADi(cyclohexylmethyl)phosphinic acid

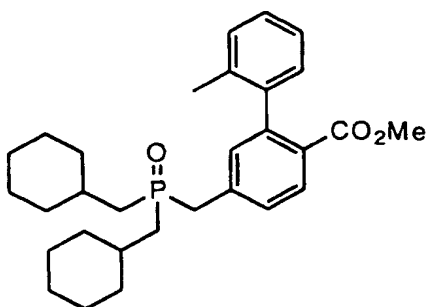
Using the Grignard reagent made from bromomethyl cyclohexane, the title compound was prepared by the method found in JACS, **72**, 5508 (1950). MS (DCI/NH₃) 259/276 (M+H)⁺/ (M+H+NH₃)⁺.

9215

Example 1214BDi(cyclohexylmethyl)phosphinic acid methyl ester

Using the compound described in Example 1214A, the title compound was prepared by the method found in JOC, **59**, 7616 (1994)-specifically Method B on p. 7623. MS (DCI/NH₃) 273/290 (M+H)⁺/ (M+H+NH₃)⁺.

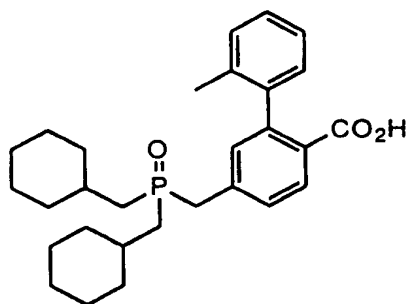
9220

Example 1214C

9225 4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

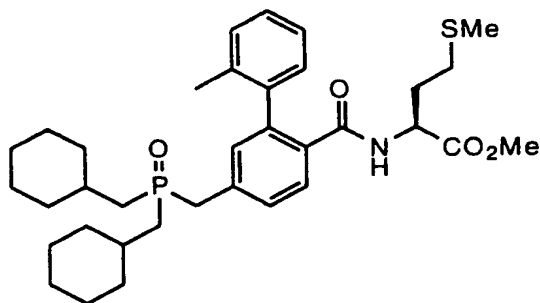
The title compound was prepared from the compound described in Example 1214B and the bromide described in Example 1178D using the method of Example 1212D. MS (APCI) 481 (M+H)⁺.

9230

Example 1214D

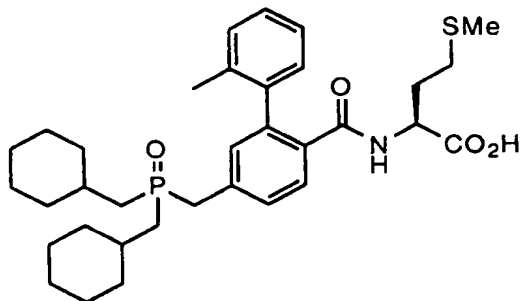
4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

9235 The title compound was prepared from the compound described in Example 1214C using the method of Example 1178H. MS (APCI) 467 (M+H)⁺.

Example 1214E

9240 N-[4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

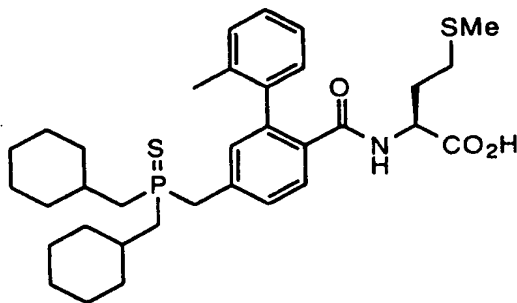
The above compound was prepared from the compound described in Example 1214D according to the method of Example 1205D. MS (APCI) 612 (M+H)⁺.



Example 1214F

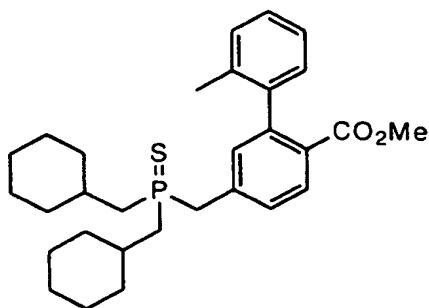
N-[4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

The above compound was prepared from the compound described in Example 1214E according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.04 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80, 1.60 (both m, total 18H), 1.20 (m, 6H), 0.95 (m, 4H). MS (ESI) 596 (M-H)⁻. Anal calcd for C₃₄H₄₈NO₄PS: C, 68.31; H, 8.09; N, 2.34. Found: C, 68.20; H, 8.19; N, 2.36.

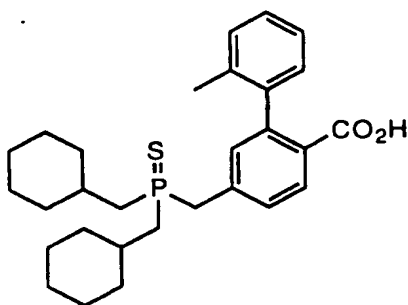


Example 1215

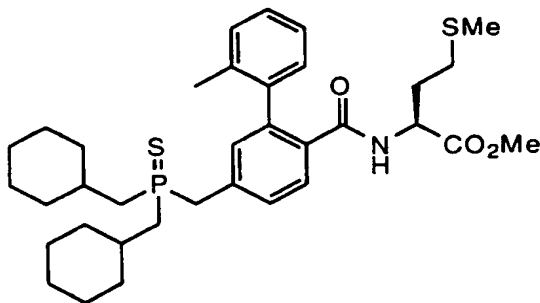
N-[4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

**Example 1215A****4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester**

The compound described in Example 1214C (390 mg, 0.81 mmol) was dissolved in CH₃CN (15 mL), then Lawesson's reagent (1.57 g, 3.88 mmol) was added. The reaction was heated under reflux for 3 h, then stirred at RT overnight. After filtration through celite and concentration of the filtrate, purification by chromatography using hex/EtOAc 85/15 gave 335 mg (83%) of the title compound. MS (APCI) 497 (M+H)⁺.

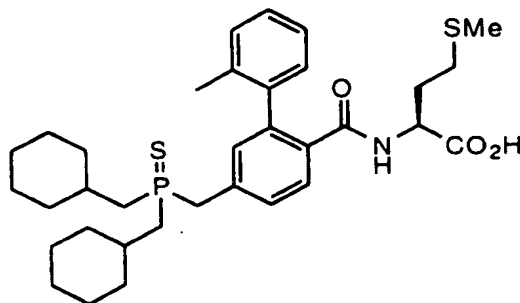
**Example 1215B****4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoic acid**

The title compound was prepared from the compound described in Example 1215A using the method of Example 1178H. MS (ESI) 483 (M+H)⁺.

**Example 1215C**

N-[4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

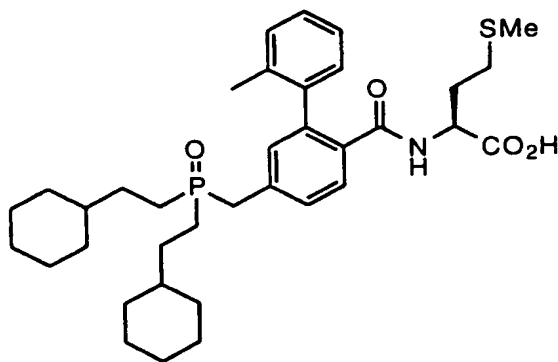
The above compound was prepared from the compound described in Example 1215B according to the method of Example 1205D. MS (APCI) 628 (M+H)⁺.



Example 1215D

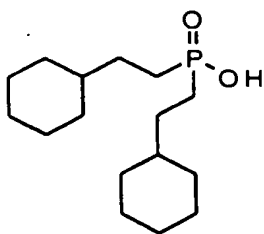
N-[4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

The above compound was prepared from the compound described in Example 1215C according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.14 (d, 1H), 7.46 (d, 1H), 7.38 (d, 1H), 7.20, 7.14 (both m, total 5H), 4.21 (m, 1H), 3.40 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80, 1.60 (both m, total 18H), 1.20, 1.00 (both m, total 10H). MS (ESI) 612 (M-H)⁻. Anal calcd for C₃₄H₄₈NO₃PS₂: C, 66.53; H, 7.88; N, 2.28. Found: C, 66.26; H, 7.86; N, 2.19.

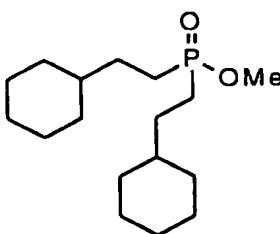


Example 1219

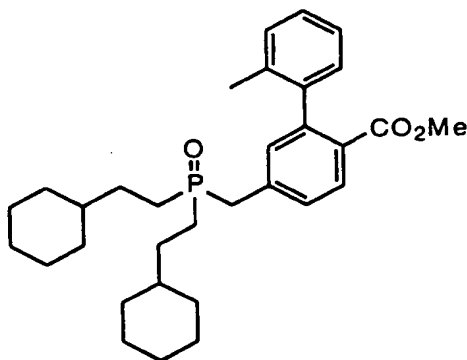
N-[4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

**Example 1219A****Di(2-cyclohexylethyl)phosphinic acid**

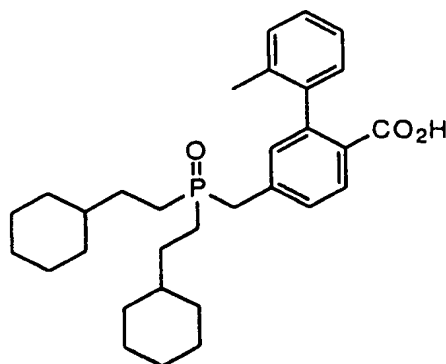
9300 The bromide described in Example 1207A was converted to the Grignard reagent, then used to prepare the title compound by the method of Example 1214A. MS (DCI/NH₃) 287/304 (M+H)⁺/ (M+H+NH₃)⁺.

**Example 1219B****Di(2-cyclohexylethyl)phosphinic acid methyl ester**

9305 Using the compound described in Example 1219A, the title compound was prepared by the method of Example 1214B. MS (DCI/NH₃) 301/318 (M+H)⁺/ (M+H+NH₃)⁺.

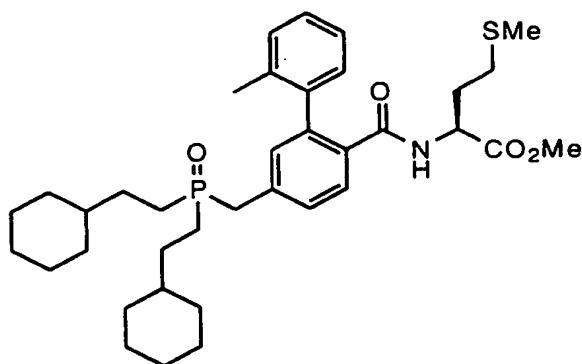
**Example 1219C****4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester**

9310 The title compound was prepared from the compound described in Example 1219B and the bromide described in Example 1178D using the method of Example 1212D. MS (APCI) 509 (M+H)⁺.

**Example 1219D**

9320 4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

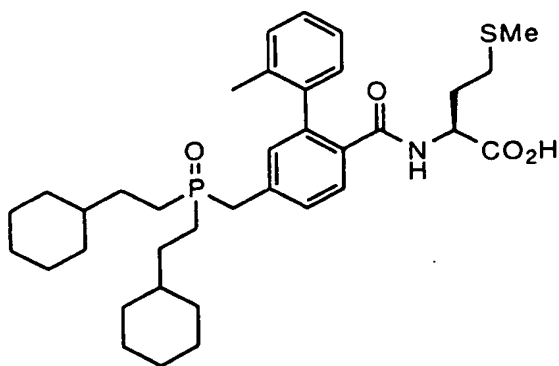
The title compound was prepared from the compound described in Example 1219C using the method of Example 1178H. MS (APCI) 495 (M+H)⁺.

**Example 1219E**

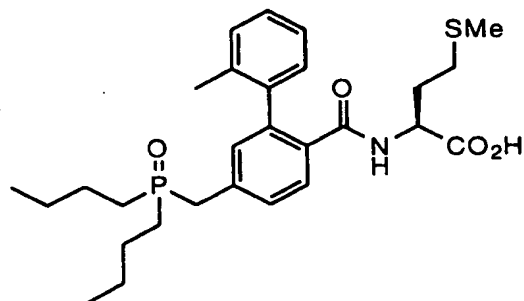
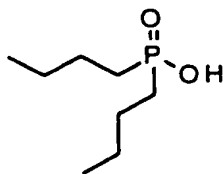
9325 N-[4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

The above compound was prepared from the compound described in Example 1219D according to the method of Example 1205D. MS (APCI) 640 (M+H)⁺.

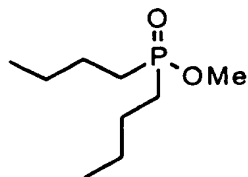
9330

Example 1219FN-[4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

The above compound was prepared from the compound described in Example 1219E according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.07 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80, 1.60 (both m, total 16H), 1.32 (m, 4H), 1.15 (m, 8H), 0.83 (m, 4H). MS (ESI) 624 (M-H)⁻. Anal calcd for C₃₆H₅₂NO₄PS: C, 69.09; H, 8.37; N, 2.24. Found: C, 68.98; H, 8.33; N, 2.20.

Example 1222N-[4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionineExample 1222ADibutylphosphinic acid

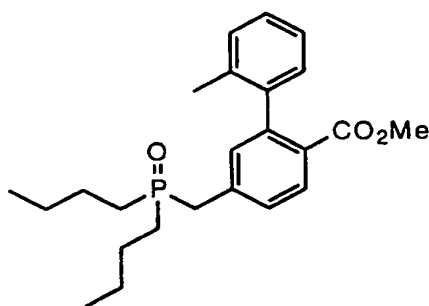
Using butylmagnesium chloride, the title compound was prepared by the method of
9350 Example 1214A. MS (DCI/NH₃) 179/196 (M+H)⁺/ (M+H+NH₃)⁺.



Example 1222B

Dibutylphosphinic acid methyl ester

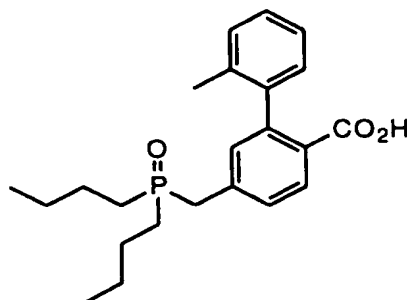
9355 Using the compound described in Example 1222A, the title compound was prepared
by the method of Example 1214B. MS (DCI/NH₃) 193/210 (M+H)⁺/ (M+H+NH₃)⁺.



Example 1222C

9360 4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

The title compound was prepared from the compound described in Example 1222B
and the bromide described in Example 1178D using the method of Example 1212D. MS
(DCI/NH₃) 401/418 (M+H)⁺/ (M+H+NH₃)⁺.



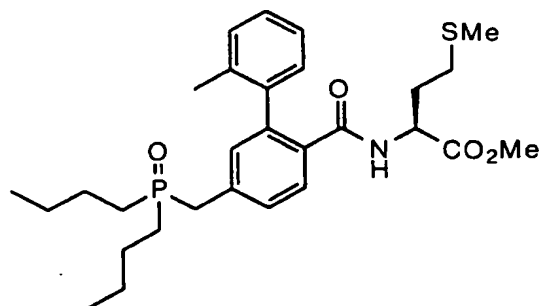
9365

Example 1222D

4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1222C
using the method of Example 1178H. MS (DCI/NH₃) 387/404 (M+H)⁺/ (M+H+NH₃)⁺.

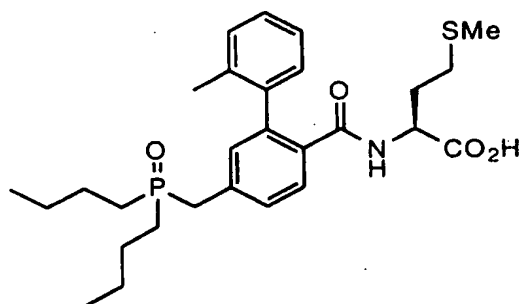
9370

**Example 1222E**

N-[4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

The above compound was prepared from the compound described in Example 1222D according to the method of Example 1205D. MS (APCI) 532 (M+H)⁺.

9375

**Example 1222F**

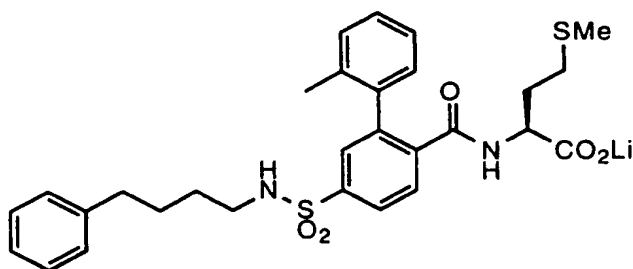
N-[4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

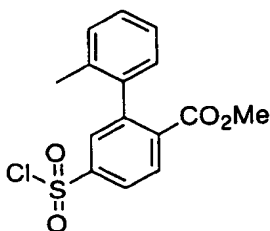
9380

The above compound was prepared from the compound described in Example 1222E according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.15 (d, 1H), 7.46 (d, 1H), 7.31 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80 (m, 2H), 1.60 (m, 4H), 1.40 (m, 8H), 0.85 (t, 6H). MS (ESI) 516 (M-H)⁻. Anal calcd for C₂₈H₄₀NO₄PS:

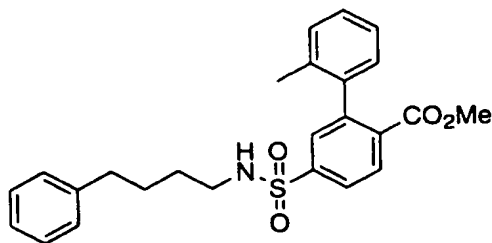
9385

C, 64.97; H, 7.79; N, 2.71. Found: C, 64.87; H, 7.83; N, 2.72.



Example 1278N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine lithium salt.Example 1278A

4-amino-2-(2-methylphenyl)benzoic acid methyl ester (4.5 g, 0.018 mol) in an excess of concentrated (38%) hydrochloric acid (25 ml), was diazotized at 0°C with sodium nitrite (1.45 g, 0.0216 mol). The solution of diazonium chloride was added with stirring to a mixture of sulfur dioxide (40 g), 1,2-dichlorobenzene (10 ml), copper(II) chloride (1.4 g), and potassium chloride (1.4 g) in dioxane (20 ml), and heated to 40-50°C. After the evolution of nitrogen was complete (about 30 min.), water (200 ml) was added and the sulfonyl chloride was extracted with methylene chloride. The organic layer was washed quickly with 10% sodium hydroxide (3*50 ml), followed by washing with water. After drying over anhydrous magnesium sulfate, the organic solvents were removed under reduced pressure. A brown liquid of the title compound (4.8 g, 82%) was obtained. ¹H NMR: 2.09(3H, s), 3.65(3H, s), 7.0-7.1(1H, d), 7.2-7.4(3H, m), 7.9-8.0(1H, d), 8.1-8.2(2H, m). ¹³C NMR: 20.0 (CH₃), 52.6 (OCH₃), 125.5, 125.6, 128.4, 129.2, 130.0, 131.0, 135.0, 135.0, 138.6, 144.2, 146.0, 166.0. (DSI/NH₃)MS: 324 (M+NH₄)⁺.

Example 1278B

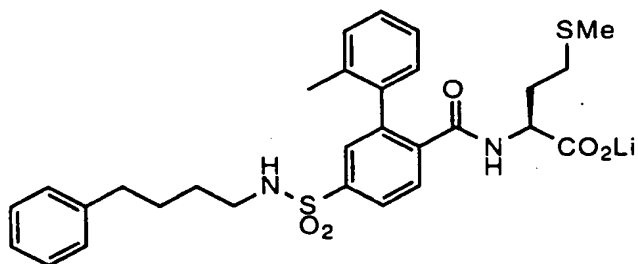
A mixture of 1278B (0.32 g, 1.0 mmol), 4-phenylbutylamine (0.223 g, 1.5 mmol), and 0.2 ml of pyridine in 5 ml of anhydrous methylene chloride was stirred for 12 hours. The reaction mixture was washed by 10% HCl, brine, and dried over anhydrous MgSO₄. Flash chromatography of the residue eluting with 4:6EtOAc/Hexane afforded 0.205 g of the title compound. NMR(CDCl₃) 8.00-8.05 (m, 1H); 7.85-7.92 (m, 1H); 7.73 (s, 1H); 7.00-

9415 7.30 (m, 8H); 4.35-4.45 (m, 1H); 3.65 (s, 3H); 2.95-3.08 (t, 2H); 2.55-2.62 (t, 2); 2.08 (s, 3H); 1.4-1.67 (m, 4H). (DSI/NH₃)MS: 455 (M+NH₄)⁺.

Example 1278C

Prepared according to the procedure of example 1258C from 1278B NMR(CDCl₃)

9420 8.00-8.10 (m, 1H); 7.88-7.94 (m, 1H); 7.73 (s, 1H); 7.10-7.40 (m, 8H); 5.93-6.00 (m, 1H); 4.52-4.60 (m, 1H); 4.32-4.40 (m, 1H); 3.70 (s, 3H); 2.95-3.08 (t, 2H); 2.55-2.62 (t, 2); 2.0-2.2 (m, 10H); 1.70-2.00 (m, 1H); 1.50-1.70 (m, 4H). (DSI/NH₃)MS: 569(M+H)⁺; 586 (M+NH₄)⁺.



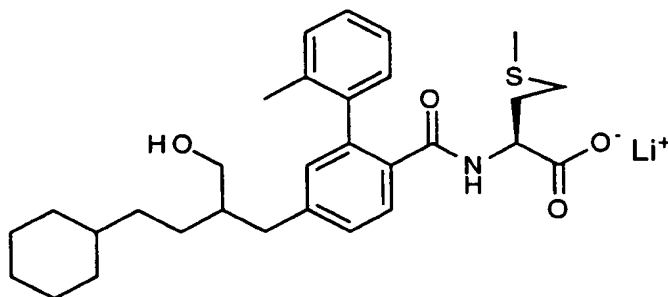
9425

Example 1278

N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine lithium salt.

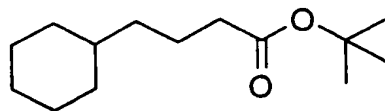
Prepared according to the procedure of example 1178J from 1296C. NMR

9430 ¹H(MeOH-d₄): 7.8-7.9 (2H, m); 7.7 (1H, s); 7.1-7.3 (13H, m); 4.2-4.3 (1H, m); 2.85-2.95 (2H, m); 2.5-2.6 (2H, m); 1.6-2.3 (14H, m). ESI(-)/MS: 553(M-Li).

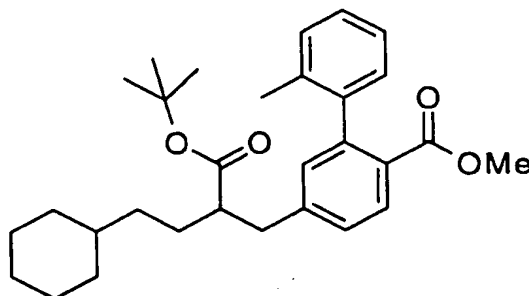


Example 1299

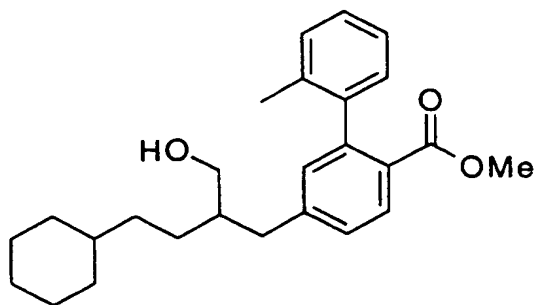
9435 N-[4-(2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

Example 1299Atert-Butyl 4-cyclohexylbutyrate

4-Cyclohexylbutyric acid (1.8 g, 10.6 mmol), isobutylene (25 mL) and concentrated sulfuric acid (0.3 mL) were combined in CH₂Cl₂ (25 mL) in a pressure bottle. After shaking for 8 days, the pressure bottle was placed in a -78 °C bath and a saturated solution of NaHCO₃ was added and the phases separated. The organic phase was dried (MgSO₄) and concentrated to afford crude ester as a clear oil (2.3 g). ¹H NMR (CDCl₃, 300 MHz) δ 0.81-0.94 (m, 2H), 1.14-1.25 (m, 6H), 1.44 (s, 9H) 1.55-1.74 (m, 7H), 2.18 (t, J=7.5 Hz, 2H); MS (CI/NH₃) m/z: (M+H)⁺ 227.

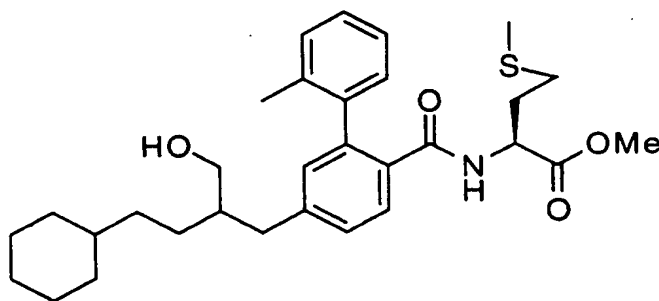
Example 1299B4-[2-(2-Cyclohexylethyl)tert-butylpropion-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

A 1.6M solution of n-BuLi in hexanes (1.7 mL, 2.7 mmol) was added to a solution of diisopropylamine (385 µL, 2.7 mmol) at ambient temperature. After 10 minutes of stirring, the solution was cooled to -78 °C and the product from Example 1299A (600 mg, 2.6 mmol) in THF (2.5 mL) was added to the reaction mixture. After stirring for 15 min, the cold bath was removed. After 30 min of stirring, the mixture was recooled to -78 °C and the product from Example 1308E (1.0 g, 2.7 mmol) in THF (2.0 mL) was added to the reaction mixture. The mixture was allowed to gradually warm to ambient temperature and stir over night. A solution of 2N HCl was added and the mixture extracted with EtOAc (2X). The organic phases were combined, dried (MgSO₄) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:40) to afford a clear oil (572 mg, 47%). MS (CI/NH₃) m/z: (M+H)⁺ 465.

Example 1299C4-[2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

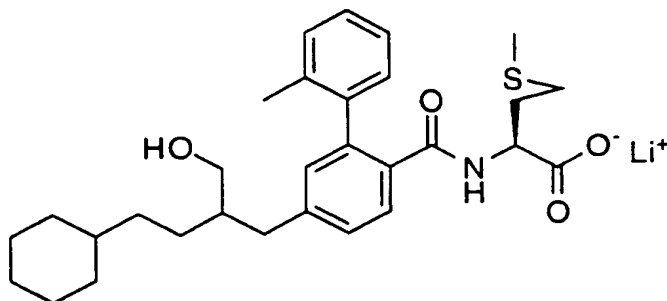
Trifluoroacetic acid (3 mL) was added to a solution of the product from Example 1299B (448 mg, 1.0 mmol) in CH₂Cl₂ (3 mL) at ambient temperature. After stirring for 90 min, solvent was evaporated to dryness. MS (CI/NH₃) m/z: (M+H)⁺ 409.

A 1.0M solution of borane THF complex (2.1 mL, 2.1 mmol) was added to a solution of the crude product described above in THF (3 mL) at ambient temperature. After stirring for 6 hours, a 2N solution of HCl was added to the reaction mixture. After 90 min of stirring, the mixture was extracted with EtOAc (2X). The organic phases were combined, dried (MgSO₄) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (256 mg, 68%). MS (CI/NH₃) m/z: (M+H)⁺ 395.

Example 1299DN-[4-[2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

The product from Example 1299C (97 mg, 0.25 mmol) was saponified in a similar manner as that described in Example 608C. The crude acid was then allowed to react with EDCI (55 mg, 0.28 mmol), Hobt (30 mg, 0.22 mmol), (L)-methionine methyl ester hydrochloride (48 mg, 0.24 mmol) and NMM (40 μL, 0.36 mmol) in DMF (1 mL) in a manner similar to that described in Example 608 D. The crude residue was chromatographed

(silica gel; EtOAc/hexanes, 1:2) to afford the title compound as a clear oil (66 mg, 63%). MS (CI/NH₃) m/z: (M+H)⁺ 526.



9490

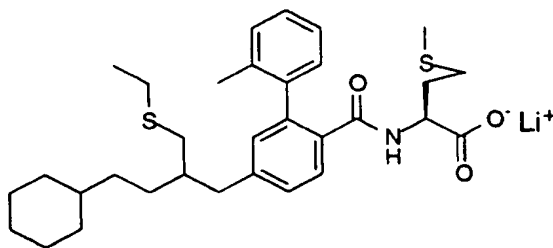
Example 1299E

N-[4-(2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine

Lithium Salt

The product from Example 1299D (60 mg, 0.11 mmol) was allowed to react with lithium hydroxide monohydrate (5 mg, 0.12 mmol) in a manner similar to that described in Example 608E to afford the title compound. ¹H NMR (DMSO-d₆, 300 MHz) δ 0.72-0.88 (m, 2H), 1.03-1.30 (m, 8H), 1.52-1.70 (m, 9H), 1.88-2.03 (m, 6H), 2.15 (m, 1H), 2.47 (m, partially buried under DMSO peak 1H), 2.70 (m, 1H), 3.32 (d, partially buried under water peak 2H), 4.42 (m, 1H), 6.90 (d, J=6 Hz, 1H), 6.94 (s, 1H), 7.10-7.25 (m, 4H), 7.46 (d, J=8 Hz, 1H); MS (APCI(-)) m/z: (M-H)⁻ 510; Anal. Calcd for C₃₀H₄₀LiNO₄S•2.1 H₂O: C, 64.87; H, 8.02; N, 2.52. Found: C, 64.89; H, 7.37; N, 2.37.

9500

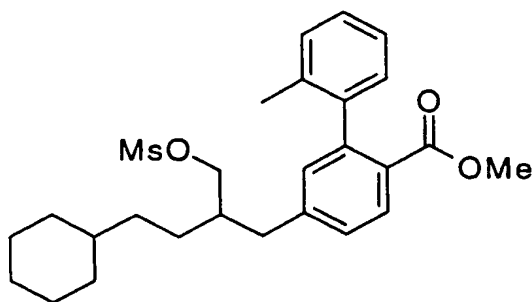


9505

Example 1300

N-[4-(2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine

Lithium Salt



9510

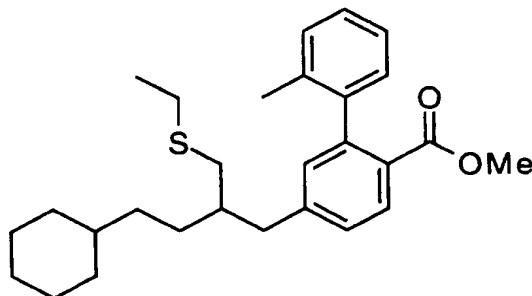
Example 1300A4-[2-(2-Cyclohexylethyl)-1-methylsulfonyloxyprop-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

9515

Methanesulfonyl chloride (33 μ L) was added to a solution of the product from Example 1299C (149 mg, 0.38 mmol) and triethylamine (60 μ L, 0.42 mmol) in THF (1 mL) at 0 $^{\circ}$ C. The reaction mixture was allowed to warm to ambient temperature and stir for 3 hours. A solution of 2N HCl was added to the mixture which was then extracted with EtOAc. The organic phase was separated, dried (MgSO_4) and concentrated. The residue

9520

was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (111 mg, 62%). ^1H NMR (CDCl_3 , 300 MHz) δ 0.75-0.90 (m, 2H), 1.07-1.27 (m, 6H), 1.35-1.43 (m, 2H), 1.60-1.66 (m, 5H), 2.04 (m, 1H), 2.05 (s, 3H), 2.66-2.81 (m, 2H), 2.96 (s, 3H), 3.61 (s, 3H), 4.10 (d, $J=5$ Hz, 2H), 7.04-7.07 (m, 2H), 7.18-7.29 (m, 4H), 7.92 (d, $J=8$ Hz, 1H); MS (CI/NH_3) m/z : ($\text{M}+\text{H}$) $^+$ 473.



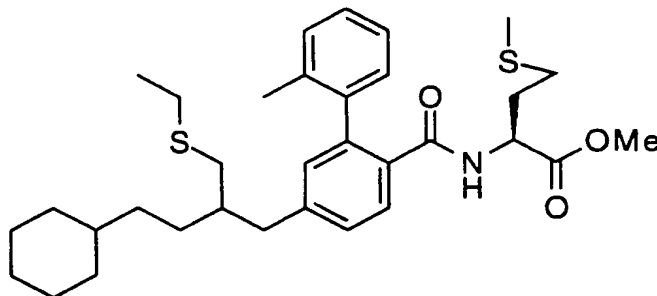
9525

Example 1300B4-[2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

9530

Ethanethiol (50 μ L, 0.66 mmol) was added to a 60% dispersion in mineral oil NaH (27 mg, 0.68 mmol) slurry in THF (0.7 mL) at ambient temperature. After stirring for 40 min, the product from Example 1300A (105 mg, 0.22 mmol) in THF (0.7 mL) was added to the reaction mixture followed by heating at reflux for 90 min. The mixture was allowed to cool to ambient temperature and a solution of 2N HCl was added to the reaction vessel. The

mixture was extracted with EtOAc (2X). The organic phases were combined, dried
 9535 (MgSO₄) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:10) to afford a clear oil (83 mg, 86%). MS (CI/NH₃) m/z: 439 (M+H)⁺.

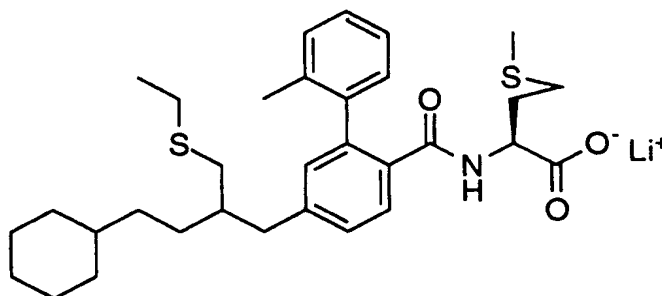


9540

Example 1300C

N-[4-(2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine
 methyl ester

The product from Example 1300B (78 mg, 0.18 mmol) was saponified in a similar
 manner as that described in Example 608C. The crude acid was then allowed to react with
 9545 EDCI (48 mg, 0.25 mmol), Hobt (27 mg, 0.20 mmol), (L)-methionine methyl ester
 hydrochloride (43 mg, 0.22 mmol) and NMM (35 μ L, 0.32 mmol) in DMF (1.0 mL) in a
 manner similar to that described in Example 608 D. The crude residue was chromatographed
 (silica gel; EtOAc/hexanes, 1:8) to afford the title compound as a clear oil (46.5 mg, 45%).



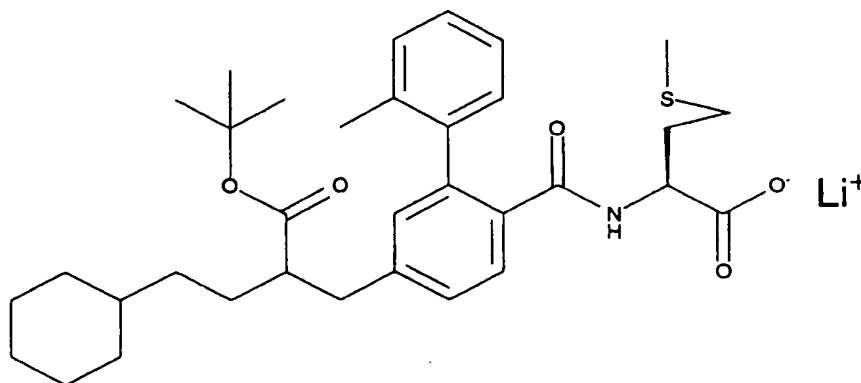
9550

Example 1300D

N-[4-(2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine
 Lithium Salt

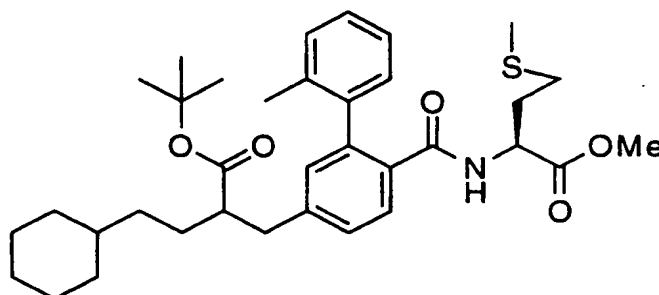
The product from Example 1300C (46.5 mg, 0.08 mmol) was allowed to react with
 9555 lithium hydroxide monohydrate (4 mg, 0.08 mmol) in a manner similar to that described in
 Example 608E to afford the title compound. ¹H NMR (DMSO-d₆, 300 MHz) δ 0.75-0.88
 (m, 2H), 1.08-1.38 (m, 10H), 1.53-2.01 (m, 14H), 2.15 (m, 1H), 2.39-2.49 (m, 4H),

2.57-2.75 (m, 2H), 3.32 (d, partially buried under water peak 2H), 3.66 (m, 1H), 6.86 (d, J=6 Hz, 1H), 6.95 (m, 1H), 7.12-7.26 (m, 4H), 7.47 (d, J=8 Hz, 1H); MS (APCI(-)) m/z: (M-H)⁻ 554; Anal. Calcd for C₃₂H₄₄LiNO₃S₂•1.75 H₂O: C, 64.78; H, 8.07; N, 2.36. Found: C, 64.75; H, 7.40; N, 2.20.



Example 1301

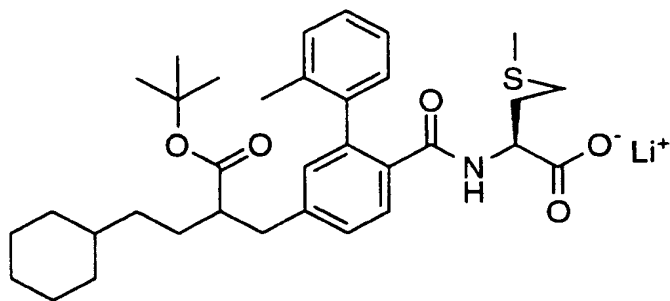
N-[4-(2-(2-cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)benzoyl]methionine
Lithium Salt



Example 1301A

N-[4-(2-(2-Cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)benzoyl]methionine
methyl ester

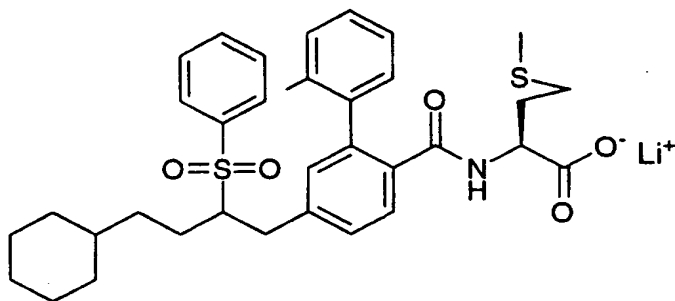
The product from Example 1299B (99 mg, 0.21 mmol) was saponified in a similar manner as that described in Example 608C. The crude acid was then allowed to react with EDCI (56 mg, 0.29 mmol), Hobt (31 mg, 0.23 mmol), (L)-methionine methyl ester hydrochloride (50 mg, 0.25 mmol) and NMM (42 μ L, 0.38 mmol) in DMF (1.0 mL) in a manner similar to that described in Example 608 D. The crude residue was chromatographed (silica gel; EtOAc/hexanes) to afford the title compound as a clear oil (62 mg, 49.5%).



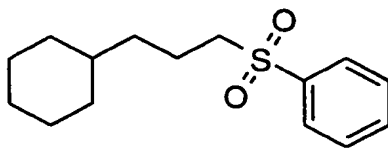
9580

Example 1301B**N-[4-(2-(2-Cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)benzoyl]methionine****Lithium Salt**

The product from Example 1301A (61 mg, 0.10 mmol) was allowed to react with
 9585 lithium hydroxide monohydrate (4.5 mg, 0.08 mmol) in a manner similar to that described
 in Example 608E to afford the title compound. ¹H NMR (DMSO-d₆, 300 MHz) δ 0.75-
 0.90 (m, 2H), 1.05-1.35 (m, 15H), 1.45-2.03 (m, 17H), 2.15 (m, 1H), 2.75-2.80 (m,
 2H), 3.65 (m, 1H), 6.86-7.00 (m, 2H), 7.07-7.25 (m, 4H), 7.46 (d, J=8 Hz, 1H); MS
 (APCI(-)) m/z: (M-H)⁻ 580; Anal. Calcd for C₃₄H₄₆LiNO₅S•1.70 H₂O: C, 66.04; H,
 9590 8.05; N, 2.26. Found: C, 66.01; H, 7.54; N, 2.27.



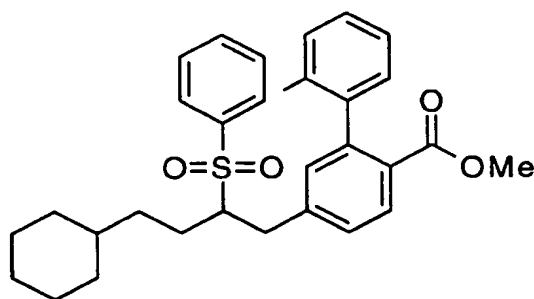
9595

Example 1302**N-[4-(4-Cyclohexyl-2-phenylsulfonyl)but-1-yl]-2-(2-methylphenyl)benzoyl]methionine****Lithium Salt**

9600

Example 1302A**3-Cyclohexylpropyl phenyl sulfone**

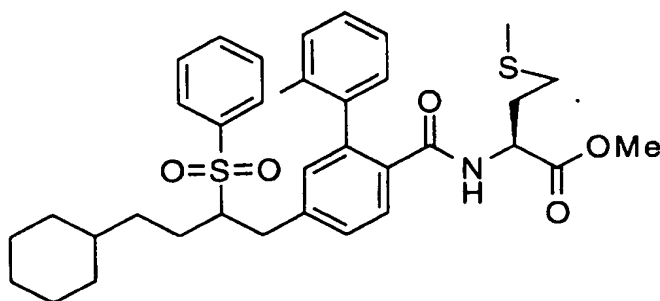
A solution of 2.5M nBuLi in hexanes (1.9 mL, 4.7 mmol) was added to a solution of diisopropylamine (660 μ L, 4.7 mmol) in THF (9.0 mL) at ambient temperature. After 10 min, the mixture was cooled to -78 °C and methyl phenyl sulfone (700 mg, 4.5 mmol) was added to the reaction vessel. The cold bath was removed and after stirring for 30 min, 1-bromo-2-cyclohexylethane (1.3 g, 6.7 mmol) was added to the reaction mixture. The mixture was allowed to warm to ambient temperature and stir for 18 hours. A solution of 2N HCl was added to the reaction mixture followed by extraction with EtOAc (2X). The organic phases were combined, dried (MgSO₄) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (620 mg, 52%). ¹H NMR (CDCl₃, MHz) δ 0.75-0.91 (m, 2H), 1.07-1.26 (m, 6H), 1.58-1.76 (m, 7H), 3.06 (t, J=8 Hz, 2H), 7.55-7.70 (m, 3H), 7.92 (m, 2H); MS (CI/NH₃) m/z: (M+NH₄)⁺ 284.



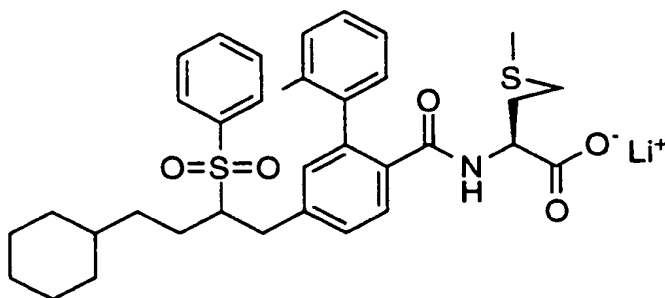
Example 1302B

N-[4-(4-Cyclohexyl-2-phenylsulfonyl)but-1-yl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

The product from Example 1302A (200 mg, 0.75 mmol) was allowed to react with diisopropylamine (110 μ L, 0.79 mmol), 1.6M nBuLi in hexanes (495 μ L, 0.79 mmol) and the product from Example 1308E (302 mg, 0.82 mmol) in a manner similar to that described under Example 1302A. The crude residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (179 mg, 47%). ¹H NMR (CDCl₃, MHz) δ 0.60-0.75 (m, 2H), 0.90-1.15 (m, 6H), 1.43 (m, 1H), 1.50-1.64 (m, 5H), 1.84 (m, 1H), 2.02 (s, 3H), 2.78 (m, 1H), 3.22 (m, 1H), 3.38 (m, 1H), 3.60 (s, 3H), 6.95-7.02 (m, 2H), 7.14-7.29 (m, 4H), 7.53-7.88 (m, 3H), 7.86-7.93 (m, 3H); MS (CI/NH₃) m/z: (M+NH₄)⁺ 522.

Example 1302CN-[4-(4-Cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

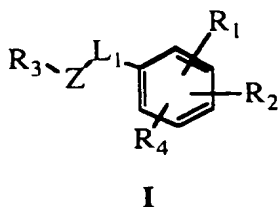
9630 The product from Example 1302B (168 mg, 0.33 mmol) was saponified in a similar manner as that described in Example 608C. The crude acid was then allowed to react with EDCI (90 mg, 0.46 mmol), Hobt (50 mg, 0.36 mmol), (L)-methionine methyl ester hydrochloride (80 mg, 0.39 mmol) and NMM (65 μ L, 0.39 mmol) in DMF (1.3 mL) in a manner similar to that described in Example 608 D. The crude residue was chromatographed
9635 (silica gel; EtOAc/hexanes, 1:4) to afford the title compound as a clear oil (117 mg, 56%).

Example 1302DN-[4-(4-Cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

9640 The product from Example 1302C (107 mg, 0.17 mmol) was allowed to react with lithium hydroxide monohydrate (8 mg, 0.18 mmol) in a manner similar to that described in Example 608E to afford the title compound. ^1H NMR (DMSO- d_6 , 300 MHz) δ 0.54-0.70 (m, 2H), 0.85-1.10 (m, 6H), 1.30-2.04 (m, 16H), 2.14 (m, 1H), 2.80 (m, 1H), 3.16 (m, 1H), 3.60-3.73 (m, 2H), 6.85-7.26 (m, 6H), 7.43 (d, $J=8$ Hz, 1H), 7.62-7.68 (m, 2H),
9645 7.75 (m, 1H), 7.93 (d, $J=7$ Hz, 2H); MS (APCI(-)) m/z : (M-H) $^-$ 620; Anal. Calcd for $\text{C}_{35}\text{H}_{42}\text{LiNO}_5\text{S}_2 \cdot 3.20 \text{ H}_2\text{O}$: C, 61.33; H, 7.12; N, 2.04. Found: C, 61.31; H, 6.63; N, 1.70

WHAT IS CLAIMED IS:

1. A compound having Formula I



or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from the group consisting of

- (1) hydrogen,
- (2) alkenyl,
- (3) alkynyl,
- (4) alkoxy,
- (5) haloalkyl,
- (6) halogen,
- (7) loweralkyl,
- (8) thioalkoxy,
- (9) aryl- L_2 - wherein aryl is selected from the group consisting of
 - (a) phenyl,
 - (b) naphthyl,
 - (c) dihydronaphthyl,
 - (d) tetrahydronaphthyl,
 - (e) indanyl, and
 - (f) indenyl

wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y,

or Z wherein X, Y, and Z are independently selected from the

group consisting of

alkenyl,

alkynyl,

alkoxy,

aryl,

carboxy,

cyano,

halogen,

haloalkyl,
 hydroxy,
 hydroxyalkyl,
 loweralkyl,
 5 nitro,
 N-protected amino, and
 -NRR' wherein R and R' are independently selected
 from the group consisting of
 hydrogen and
 10 loweralkyl,
 oxo (=O), and
 thioalkoxy and

L₂ is absent or is selected from the group consisting of

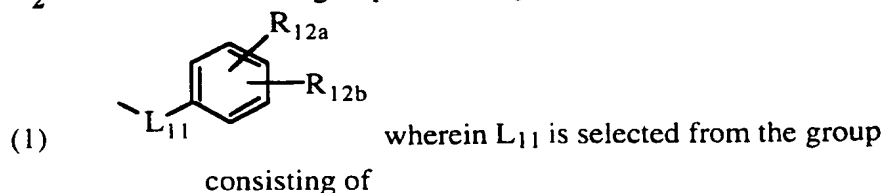
-CH₂-,
 15 -CH₂CH₂-,
 -CH(CH₃)-,
 -O-,
 -C(O)-,
 -S(O)_q wherein q is 0, 1 or 2, and
 20 -N(R)-, and

(10) heterocycle-L₂- wherein L₂ is as defined above and the heterocycle is
 unsubstituted or substituted with 1, 2, 3 or 4 substituents
 independently selected from the group consisting of

- (a) loweralkyl,
- 25 (b) hydroxy,
- (c) hydroxyalkyl,
- (d) halogen
- (e) cyano,
- (f) nitro,
- 30 (g) oxo (=O),
- (h) -NRR',
- (i) N-protected amino,
- (j) alkoxy,
- (k) thioalkoxy,
- 35 (l) haloalkyl,
- (m) carboxy, and

(n) aryl;

R_2 is selected from the group consisting of



- (a) a covalent bond,
- (b) $-C(W)N(R)-$ wherein R is defined previously and W is selected from the group consisting of O and S,
- (c) $-C(O)-$,
- (d) $-N(R)C(W)-$,
- (e) $-CH_2O-$,
- (f) $-C(O)O-$, and
- (g) $-CH_2N(R)-$,

R_{12a} is selected from the group consisting of

- (a) hydrogen,
- (b) loweralkyl, and
- (c) $-C(O)OR_{13}$ wherein R_{13} is selected from the group consisting of hydrogen and a carboxy-protecting group, and

R_{12b} is selected from the group consisting of

- (a) hydrogen and
 - (b) loweralkyl,
- with the proviso that R_{12a} and R_{12b} are not both hydrogen,

(2) $-L_{11}-C(R_{14})(R_v)-C(O)OR_{15}$ wherein L_{11} is defined previously,

R_v is selected from the group consisting of

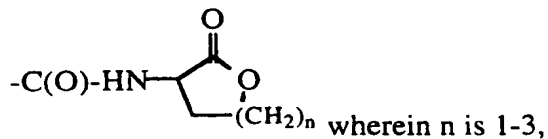
- (a) hydrogen and
- (b) loweralkyl,

R_{15} is selected from the group consisting of

- (a) hydrogen,
- (b) alkanoyloxyalkyl,
- (c) loweralkyl, and
- (b) a carboxy-protecting group, and

R_{14} is selected from the group consisting of

- (a) alkoxyalkyl,
- (b) alkoxyarylalkyl,
- (c) alkoxycarbonylalkyl,
- (d) alkylsulfinylalkyl,
- (e) alkylsulfonylalkyl,
- (f) alkynyl,
- (g) aminoalkyl,
- (h) aminocarbonylalkyl,
- (i) aminothiocabonylalkyl,
- (j) aryl,
- (k) arylalkyl,
- (l) carboxyalkyl,
- (m) cyanoalkyl,
- (n) cycloalkyl,
- (o) cycloalkylalkoxyalkyl,
- (p) cycloalkylalkyl,
- (q) (heterocyclic)alkyl,
- (r) hydroxyalkyl,
- (s) hydroxyarylalkyl,
- (t) loweralkyl,
- (u) sulfhydrylalkyl,
- (v) thioalkoxyalkyl wherein the thioalkoxyalkyl is
unsubstituted or substituted with 1, 2, 3, or 4
substituents selected from the group consisting of
halogen,
- (w) thioalkoxyalkylamino, and
- (x) thiocycloalkyloxyalkyl,



- (4) $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$ wherein R_{14} is defined previously
and R_{16} is selected from the group consisting of
- (a) loweralkyl,

- (b) haloalkyl,
- (c) aryl wherein the aryl is unsubstituted or substituted with
1, 2, 3, 4, or 5 substituents independently
selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR'
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl, and
- (d) heterocycle wherein the heterocycle is unsubstituted or
substituted with substituents independently
selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl;

(5) -C(O)NH-CH(R₁₄)-tetrazolyl wherein the tetrazole ring is unsubstituted or substituted with loweralkyl or haloalkyl,

(6) -L₁₁-heterocycle,

(7) -C(O)NH-CH(R₁₄)-C(O)NR₁₇R₁₈ wherein R₁₄ is defined previously and R₁₇ and R₁₈ are independently selected from the group consisting of

- (a) hydrogen,
- (b) loweralkyl,
- (c) arylalkyl,
- (d) hydroxy, and
- (e) dialkylaminoalkyl,

(8) -C(O)OR₁₅, and

(9) -C(O)NH-CH(R₁₄)-heterocycle wherein R₁₄ is as previously defined and the heterocycle is unsubstituted or substituted with loweralkyl or haloalkyl;

L₁ is absent or is selected from the group consisting of

(1) -L₄-N(R₅)-L₅- wherein L₄ is absent or selected from the group consisting of

- (a) C₁-to-C₁₀-alkylene and
- (b) C₂-to-C₁₆-alkenylene,

wherein the alkylene and alkenylene groups are unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

alkenyl,
alkenyloxy,
alkenyloxyalkyl,
alkenyl[S(O)_q]alkyl,
alkoxy,

alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2 hydroxyl substituents, with the proviso that no two hydroxyls are attached to the

same carbon,
alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1, 2, or 3
substituents independently selected from the
group consisting of
halogen and
cycloalkyl,
alkylsilyloxy,
alkyl[S(O)_q],
alkyl[S(O)_q]alkyl,
aryl wherein the aryl is unsubstituted or substituted with
1, 2, 3, 4, or 5 substituents independently
selected from the group consisting of
alkoxy wherein the alkoxy is unsubstituted or
substituted with substituents selected
from the group consisting of cycloalkyl,
aryl,
arylalkyl,
aryloxy wherein the aryloxy is unsubstituted or
substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of,
halogen,
nitro, and
-NRR',
cycloalkyl,
halogen,
loweralkyl,
hydroxyl,
nitro,
-NRR', and
-SO₂NRR',
arylalkoxy wherein the arylalkoxy is unsubstituted or
substituted with substituents selected from the
group consisting of alkoxy,
arylalkyl,

arylalkyl[S(O)_q]alkyl,

aryl[S(O)_q],

aryl[S(O)_q]alkyl wherein the aryl[S(O)_q]alkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
substituents independently selected from
alkoxy and
loweralkyl,

arylalkoxyalkyl wherein the arylalkoxyalkyl is
unsubstituted or substituted with substituents
selected from the group consisting of
alkoxy, and
halogen,

aryloxy,

aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or
substituted with substituents selected from the
group consisting of halogen,

carboxyl,

-C(O)NR_CR_D wherein R_C and R_D are independently
selected from the group consisting of
hydrogen,
loweralkyl, and
alkoxycarbonyl or

R_C and R_D together with the nitrogen to which
they are attached form a ring selected
from the group consisting of
morpholine,
piperidine,
pyrrolidine
thiomorpholine,
thiomorpholine sulfone, and
thiomorpholine sulfoxide,
wherein the ring formed by R_C and R_D

together is unsubstituted or
substituted with 1 or 2
substituents independently
selected from the group consisting

of alkoxy and alkoxyalkyl,
cycloalkenyl wherein the cycloalkenyl is unsubstituted or
substituted with 1 or 2 substituents selected from
the group consisting of alkenyl,
5 cycloalkoxy,
cycloalkoxycarbonyl,
cycloalkoxyalkyl,
cycloalkyl wherein the cycloalkyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
10 independently selected from the group consisting
of aryl,
loweralkyl, and
alkanoyl,
cycloalkylalkoxy,
15 cycloalkylalkoxycarbonyl,
cycloalkylalkoxyalkyl,
cycloalkylalkyl,
cycloalkyl[S(O)_q]alkyl,
cycloalkylalkyl[S(O)_q]alkyl,
20 fluorenyl,
heterocycle wherein the heterocycle is unsubstituted or
substituted with 1, 2, 3, or 4 substituents
independently selected from the group
consisting of
25 alkoxy wherein the alkoxy is unsubstituted or
substituted with 1 or 2 substituents
independently selected from the group
consisting of aryl and cycloalkyl,
alkoxyalkyl wherein the alkoxyalkyl is
30 unsubstituted or substituted with 1 or 2
substituents independently selected from
the group consisting of
aryl and
cycloalkyl,
35 alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1 or 2

substituents independently selected from
the group consisting of
aryl and
cycloalkyl,

5 aryl wherein the aryl is unsubstituted or
substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of
alkanoyl,
10 alkoxy,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
15 nitro,
-NRR', and
thioalkoxy,

arylalkyl,
aryloxy,
20 cycloalkoxyalkyl,
cycloalkyl,
cycloalkylalkyl,
halogen,
heterocycle,
25 hydroxyl,

loweralkyl wherein the loweralkyl is
unsubstituted or substituted with 1, 2, or
3 substituents independently selected
from the group consisting of
30 heterocycle,
hydroxyl,
with the proviso that no two hydroxyls
are attached to the same carbon,
and
35 -NRR³R^{3'} wherein R³ and R^{3'} are
independently selected from the

group consisting of
hydrogen
aryl,
loweralkyl,
5 aryl,
arylalkyl,
heterocycle,
(heterocyclic)alkyl,
cycloalkyl, and
10 cycloalkylalkyl, and
sulfhydryl,
(heterocyclic)alkoxy,
(heterocyclic)alkyl,
(heterocyclic)alkyl[S(O)_q]alkyl,
15 (heterocyclic)oxy,
(heterocyclic)alkoxyalkyl,
(heterocyclic)oxyalkyl,
heterocycle[S(O)_q]alkyl,
hydroxyl,
20 hydroxyalkyl,
imino,
N-protected amino,
=N-O-aryl, and
=N-OH,
25 =N-O-heterocycle wherein the heterocycle is
unsubstituted or substituted with 1, 2, 3, or 4
substituents independently selected from the
group consisting of
loweralkyl,
30 hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
35 oxo (=O),
-NRR'

N-protected amino,
 alkoxy,
 thioalkoxy,
 haloalkyl,
 carboxy, and
 aryl,
 =N-O-loweralkyl,
 -NR^{R3}R^{R3'},
 -NHNRCRD,
 -OG wherein G is a hydroxyl protecting group,
 -O-NH-R,

$$\text{--O--N}=\begin{matrix} \text{J'} \\ \diagup \\ \text{J} \end{matrix}$$
 wherein J and J' are independently selected
 from the group consisting of
 loweralkyl and
 arylalkyl,
 oxo,
 oxyamino(alkyl)carbonylalkyl,
 oxyamino(arylalkyl)carbonylalkyl,
 oxyaminocarbonylalkyl,
 -SO₂-A wherein A is selected from the group
 consisting of
 loweralkyl,
 aryl, and
 heterocycle
 wherein the loweralkyl, aryl, and heterocycle are
 unsubstituted or substituted with 1, 2, 3,
 4, or 5 substituents independently
 selected from the group consisting of
 alkoxy,
 halogen,
 haloalkyl,
 loweralkyl, and
 nitro,
 sulfhydryl,
 thioxo, and

thioalkoxy,

L_5 is absent or selected from the group consisting of

(a) C_1 -to- C_{10} -alkylene and

(b) C_2 -to- C_{16} -alkenylene

wherein (a) and (b) are unsubstituted or substituted as defined previously, and

R_5 is selected from the group consisting of

hydrogen,

alkanoyl wherein the alkanoyl is unsubstituted or

substituted with substituents selected from the group consisting of aryl,

alkoxy,

alkoxyalkyl,

alkoxycarbonyl wherein the alkoxycarbonyl is

unsubstituted or substituted with 1, 2 or 3 substituents independently selected from the group consisting of

aryl and

halogen,

alkylaminocarbonylalkyl wherein the

alkylaminocarbonylalkyl is unsubstituted or substituted with 1 or 2 substituents

independently selected from the group consisting of aryl,

(anthracenyl)alkyl,

aryl,

arylalkoxy,

arylalkyl wherein the arylalkyl is unsubstituted or

substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

alkoxy,

aryl,

carboxyl,

cyano,

halogen,

haloalkoxy,
haloalkyl,
nitro,
oxo, and
-L₁₁-C(R₁₄)(R_v)-C(O)OR₁₅,
(aryl)oyl wherein the (aryl)oyl is unsubstituted or
substituted with substituents selected from the
group consisting of halogen,
aryloxy carbonyl,
carboxaldehyde,
-C(O)NRR',
cycloalkoxycarbonyl,
cycloalkylaminocarbonyl,
cycloalkylaminothiocarbonyl,
cyanoalkyl,
cycloalkyl,
cycloalkylalkyl wherein the cycloalkylalkyl is
unsubstituted or substituted with 1 or 2 hydroxyl
substituents,
with the proviso that no two hydroxyls are attached to the
same carbon,
(cycloalkyl)oyl,
(9,10-dihydroanthracenyl)alkyl wherein the
(9,10-dihydroanthracenyl)alkyl is unsubstituted
or substituted with 1 or 2 oxo substituents,
haloalkyl,
heterocycle,
(heterocyclic)alkyl wherein the (heterocyclic)alkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
substituents selected from the group consisting of
loweralkyl,
(heterocyclic)oyl,
loweralkyl, wherein the loweralkyl is unsubstituted
or substituted with substituents selected from the
group consisting of -NRR',
-SO₂-A, and

thioalkoxyalkyl;

(2) $-L_4-O-L_5-$,

(3) $-L_4-S(O)_m-L_5-$ wherein L_4 and L_5 are defined previously and m is 0, 1, or 2,

(4) $-L_4-L_6-C(W)-N(R_6)-L_5-$ wherein L_4 , W , and L_5 are defined previously, R_6 is selected from the group consisting of

- (a) hydrogen,
- (b) loweralkyl,
- (c) aryl,
- (d) arylalkyl,
- (e) heterocycle,
- (f) (heterocyclic)alkyl,
- (g) cyclolakyl, and
- (h) cycloalkylalkyl, and

L_6 is absent or is selected from the group consisting of

- (a) $-O-$,
- (b) $-S-$, and
- (c) $-N(R_6)-$ wherein R_6 is selected from the group

consisting of
hydrogen,
loweralkyl,
aryl,
arylalkyl,
heterocycle,
(heterocyclic)alkyl,
cyclolakyl, and
cycloalkylalkyl,

(5) $-L_4-L_6-S(O)_m-N(R_5)-L_5-$,

(6) $-L_4-L_6-N(R_5)-S(O)_m-L_5-$,

(7) $-L_4-N(R_5)-C(W)-L_7-L_5-$ wherein L_4 , R_5 , W , and L_5 are

defined previously and L_7 is absent or is selected from the group consisting of -O- and -S-,

- (8) C_1 - C_{10} -alkylene wherein the alkylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

- (a) aryl,
- (b) arylalkyl,
- (c) heterocycle,
- (d) (heterocyclic)alkyl,
- (e) cyclolakyl,
- (f) cycloalkylalkyl,
- (g) alkylthioalkyl, and
- (h) hydroxy,

- (9) C_2 -to- C_{10} -alkenylene wherein the alkenylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

- (a) aryl,
- (b) arylalkyl,
- (c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,
- (d) heterocycle,
- (e) (heterocycle)alkyl,
- (f) hydroxyalkyl,
- (g) cyclolakyl,
- (h) cycloalkylalkyl,
- (i) alkylthioalkyl, and
- (j) hydroxy,

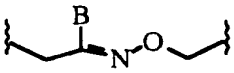
- (10) C_2 -to- C_{10} -alkynylene wherein the alkynylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

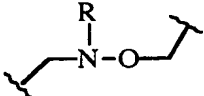
- (a) aryl,

- (b) arylalkyl,
- (c) heterocycle,
- (d) (heterocyclic)alkyl,
- (e) cyclolakyl,
- (f) cycloalkylalkyl,
- (g) alkylthioalkyl, and
- (h) hydroxy,

(11) -L₄-heterocycle-L₅-,

(12) a covalent bond,

(13)  wherein B is selected from the group consisting of loweralkyl and arylalkyl, and

(14)  ;

Z is selected from the group consisting of

- (1) a covalent bond,
- (2) -O-,
- (3) -S(O)_q-, and
- (4) -NR_z- wherein R_z is selected from the group consisting of
 - (a) hydrogen
 - (b) loweralkyl,
 - (c) aryl,
 - (d) arylalkyl,
 - (e) heterocycle,
 - (f) (heterocyclic)alkyl,
 - (g) cyclolakyl, and
 - (h) cycloalkylalkyl;

R₃ is selected from the group consisting of

- (1) hydrogen,

- (2) aryl,
- (3) fluorenyl,
- (4) heterocycle,

wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5

substituents independently selected from the group consisting of

(a) alkanoyl,

(b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

halogen,

aryl, and

cycloalkyl,

(c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2, 3, 4 or 5 substituents

independently selected from the group consisting of

aryl and

cycloalkyl,

(d) alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents

independently selected from the group consisting of

aryl, and

cycloalkyl,

(e) alkylsilyloxyalkyl,

(f) arylalkyl,

(g) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

alkanoyl,

alkoxy wherein the alkoxy is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of cycloalkyl,

carboxaldehyde,

haloalkyl,

halogen,

loweralkyl,

nitro,

-NRR', and
thioalkoxy,

(h) arylalkyl,

(i) aryloxy wherein the aryloxy is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of,
halogen,
nitro, and
-NRR',

(j) (aryl)oyl,

(k) carboxaldehyde,

(l) carboxy,

(m) carboxyalkyl,

(n) -C(O)NRR" wherein R is defined previously and R" is
selected from the group consisting of
hydrogen,
loweralkyl, and
carboxyalkyl,

(o) cyano,

(p) cyanoalkyl,

(q) cycloalkyl,

(r) cycloalkylalkyl,

(s) cycloalkoxyalkyl,

(t) halogen,

(u) haloalkyl wherein the haloalkyl is unsubstituted or substituted
with 1, 2, 3, 4, or 5 hydroxyl substituents,
with the proviso that no two hydroxyls are attached to the same
carbon,

(v) heterocycle,

(w) hydroxyl,

(x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or
substituted with substituents selected from the group
consisting of aryl,

(y) loweralkyl wherein the loweralkyl is unsubstituted or substituted
with substituents selected from the group consisting of
heterocycle,

hydroxyl,
with the proviso that no two hydroxyls are attached to the
same carbon,

-NRR³RR^{3'}, and

-P(O)(OR)(OR'),

(z) nitro,

(aa) -NRR',

(bb) oxo,

(cc) -SO₂NR_A'R_B' wherein R_A' and R_B' are independently selected

from the group consisting of

hydrogen,

(aryl)oyl,

loweralkyl, and

heterocycle wherein the heterocycle is unsubstituted or

substituted with 1, 2, or 3 substituents

independently selected from the group consisting
of loweralkyl,

(dd) sulfhydryl, and

(ee) thioalkoxy,

(5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with
1, 2, 3, 4 or 5 substituents selected from the group consisting of

(a) alkoxy,

(b) aryl,

(c) arylalkoxy

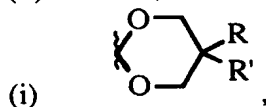
(d) aryloxy wherein the aryloxy is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
selected from the group consisting of halogen,

(e) loweralkyl,

(f) halogen,

(g) NRR³RR^{3'},

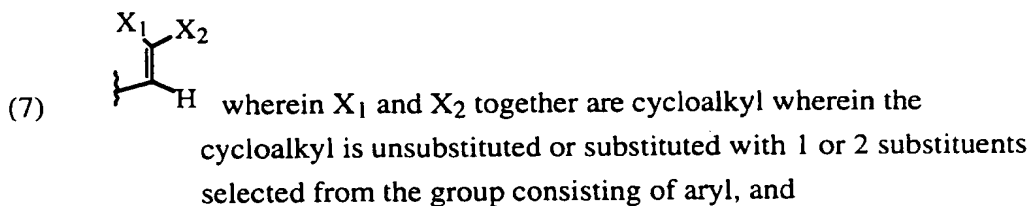
(h) oxo, and



(6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted

with 1, 2, 3 or 4 substituents independently selected from the group consisting of

- (a) loweralkyl,
- (b) alkoxy,
- (c) halogen,
- (d) aryl,
- (e) aryloxy,
- (f) alkanoyl, and
- (g) $\text{NR}^{\text{R3}}\text{R}^{\text{R3'}}$,



- (8) $-\text{P}(\text{W})\text{R}^{\text{R3}}\text{R}^{\text{R3'}}$; and

R_4 is selected from the group consisting of

- (1) hydrogen,
- (2) loweralkyl,
- (3) haloalkyl
- (4) halogen,
- (5) aryl,
- (6) arylalkyl,
- (7) heterocycle,
- (8) (heterocyclic)alkyl
- (9) alkoxy, and
- (10) $-\text{NRR}'$; or

L_1 , Z , and R_3 together are selected from the group consisting of

- (1) aminoalkyl,
- (1) haloalkyl,
- (2) halogen,
- (3) carboxaldehyde, and
- (4) (carboxaldehyde)alkyl, and

(5) hydroxyalkyl,

with the proviso that when L_1 , Z , and R_3 together are (1)-(5), R_1 is other than hydrogen.

2. A compound according to claim 1 wherein L_1 is selected from the group consisting of

(1) $-L_4-L_6-S(O)_m-N(R_5)-L_5-$,

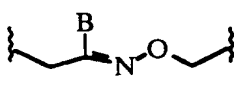
(2) $-L_4-L_6-N(R_5)-S(O)_m-L_5-$,

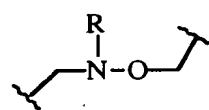
(3) C_1-C_{10} -alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,

(4) C_2 -to- C_{16} -alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,

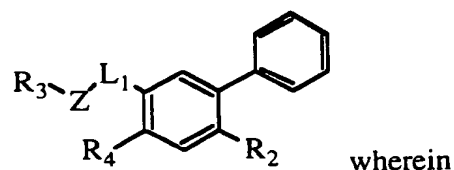
(5) C_2 -to- C_{10} -alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

(6) a covalent bond,

(7) , and

(8) .

3. A compound according to claim 1 of formula



R_3 is selected from the group consisting of

(1) hydrogen,

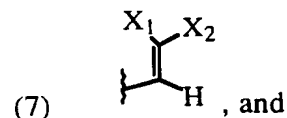
(2) aryl,

- (3) fluorenyl,
- (4) heterocycle

wherein (2)-(4) are unsubstituted or substituted as defined previously,

- (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and

- (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously,



- (8) -P(W)R³R^{3'}; and

L₁ is selected from the group consisting of

- (1) -L₄-L₆-S(O)_m-N(R₅)-L₅-,

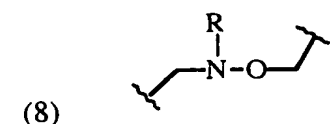
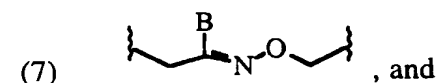
- (2) -L₄-L₆-N(R₅)-S(O)_m-L₅-,

- (3) C₁-C₁₀-alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,

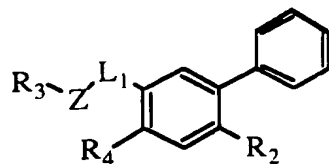
- (4) C₂-to-C₁₆-alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,

- (5) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

- (6) a covalent bond,



- 4. A compound according to claim 1 of formula



wherein

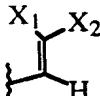
R₃ is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- (3) fluorenyl,

wherein (2) and (3) are unsubstituted or substituted as defined previously,

- (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and

- (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously,

- (6)  , and

- (7) -P(W)R³R^{3'}; and

L₁ is selected from the group consisting of

- (1) -L₄-L₆-S(O)_m-N(R₅)-L₅-,

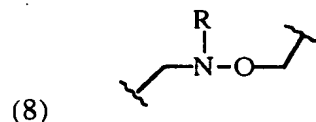
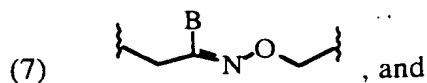
- (2) -L₄-L₆-N(R₅)-S(O)_m-L₅-,

- (3) C₁-C₁₀-alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,

- (4) C₂-to-C₁₆-alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,

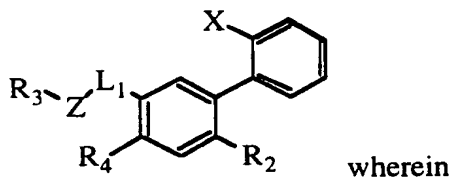
- (5) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

- (6) a covalent bond,



5. A compound according to claim 3 selected from the group consisting of
 [4-((2S,5S)-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine,
 hydrochloride ,
 [4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine,
 (4-piperazinylmethyl-2-phenylbenzoyl)methionine, and
 [4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine.

6. A compound according to claim 1 of formula



R₃ is selected from the group consisting of

- (1) hydrogen,
 (2) aryl,
 (3) fluorenyl,
 (4) heterocycle

wherein (2)-(4) are unsubstituted or substituted as defined previously,

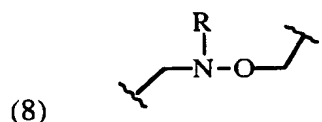
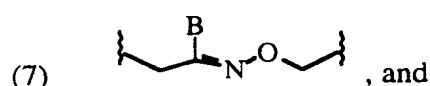
- (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and
 (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously;

L₁ is selected from the group consisting of

- (1) -L₄-L₆-S(O)_m-N(R₅)-L₅-,
 (2) -L₄-L₆-N(R₅)-S(O)_m-L₅-,

- 20 (3) C₁-C₁₀-alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,
- (4) C₂-to-C₁₆-alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,
- 25 (5) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

(6) a covalent bond,



35 Z is a covalent bond; and

X is selected from the group consisting of

alkoxy,

aryl,

40 carboxy,

cyano,

halogen,

haloalkyl,

hydroxy,

45 hydroxyalkyl,

loweralkyl,

nitro,

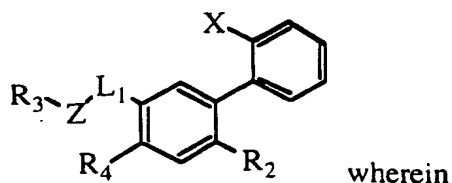
N-protected amino,

-NRR,

50 oxo (=O), and

thioalkoxy.

7. A compound according to claim 1 of formula



R₃ is selected from the group consisting of

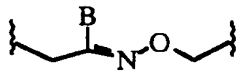
- (1) hydrogen,
- (2) aryl,
- (3) fluorenyl,

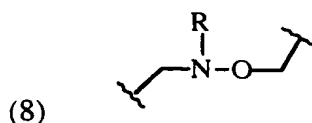
wherein (2) and (3) are unsubstituted or substituted as defined previously,

- (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and
- (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously;

L₁ is selected from the group consisting of

- (1) -L₄-L₆-S(O)_m-N(R₅)-L₅-,
- (2) -L₄-L₆-N(R₅)-S(O)_m-L₅-,
- (3) C₁-C₁₀-alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,
- (4) C₂-to-C₁₆-alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,
- (5) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,
- (6) a covalent bond,

- (7) , and



Z is a covalent bond; and

X is selected from the group consisting of

alkoxy,

aryl,

carboxy,

cyano,

halogen,

haloalkyl,

hydroxy,

hydroxyalkyl,

loweralkyl,

nitro,

N-protected amino,

-NRR,

oxo (=O), and

thioalkoxy.

8. A compound according to claim 5 wherein **X** is selected from the group consisting of loweralkyl.
9. A compound according to claim 7 selected from the group consisting of
 - [4-(5-cyclohexylmethyloxazolid-2-on-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
 - N-[4-(2-(2-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,
 - lithium salt,
 - N-[4-(2-(2-phenoxyphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-methionine,
 - lithium salt,
 - N-[4-(2-(2-phenoxyphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
 - N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,
 - lithium salt,

- N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
- 15 N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine , lithium salt,
- 20 N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
- N-[4-(2-(4-cyclohexylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine , lithium salt,
- 25 N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
- N-[4-(2-fluoren-4-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 30 N-[4-(2-naphth-2-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(2-naphth-1-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 35 N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(3-phenylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(3-naphth-2-ylpropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 40 N-[4-(3-cyclohexylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(4-phenylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(4-naphth-2-ylbut-4-on-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 45 N-[4-(4-naphth-2-ylbut-4-ol-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(4-cyclohexylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,

N-[4-(4-cyclohexylbutyl)-2-(2-methylphenyl)benzoyl]methionine sodium salt,
50 N-[4-(5-phenylpent-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-pyrimidin-5-ylethynyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(2-pyrimidin-5-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
55 N-[4-(2-pyrazin-2-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(3-naphth-2-ylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(2,3-diphenylpropan-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
60 lithium salt,
N-[4-(N-benzyl-N-phenylaminosulfonyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-2-cyclohexylethylaminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
65 N-[4-(1-benzylpiperidin-4-ylaminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-N-(2-piperidin-1-ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-N-(2-morpholin-1-ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,
70 lithium salt,
N-[4-(2-(3,4-dimethoxyphenyl)ethylaminosulfonyl)-2-phenylbenzoyl]-
methionine, lithium salt,
N-[4-(3-(2-methylpiperidin-1-yl)propylaminosulfonyl)-2-phenylbenzoyl]-
methionine, lithium salt,
75 N-[4-iodo-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
N-[4-(2-(thiazol-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(2-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
80 N-[4-(3-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-phenylcyclohexylidenyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,

- 85 N-[4-syn-(4-phenylcyclohexylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-phenylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-(3-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,
90 lithium salt,
N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-(3-phenoxy pyridazin-6-yl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
95 N-[4-(2-(3-phenoxy pyridazin-6-yl)ethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethyl)-2-(2-methylphenyl)benzoyl]-
100 methionine, lithium salt,
N-[4-(2-benzoyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine ,
N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine,
105 N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(2-(4-(2-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(2-(4-(2-aminophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-
110 methionine,
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
115 N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(2-(4-(3-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(4-t-butoxycarbonylpiperazin-1-ylmethyl)-2-(2-methylphenyl)-

- 120 benzoyl]methionine,
N-[4-(4-phenylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-N-(1,3-diphenylpropan-2-yl)iminooxymethyl-2-(2-methylphenyl)
benzoyl]-methionine, lithium salt,
- 125 N-[4-(N-hept-4-ylaminooxymethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(3-benzyloxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine ,
N-[4-(3-benzyloxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
- 130 methionine ,
N-[4-(3-cyclohexylmethoxypiperidin-1-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine ,
N-[4-(2-phenoxyethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine ,
- 135 N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine ,
N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine ,
N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-
- 140 benzoyl]methionine, lithium salt,
N-[4-(4-benzylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(4-benzylpiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
- 145 N-[4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-(4-cyclohexylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]-
- 150 methionine, lithium salt,
N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
- 155 N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-

methionine,

N-[4-(2cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,

N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,

N-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,

N-[4-(2(S)-cyclohexylmethoxymethylazetidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,

N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,

N-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,

N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-
2-(2-methylphenyl)benzoyl]methionine,

N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine,

N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,

N-[4-(2-benzyloxymethyl-4-methoxypyrrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,

N-[4-(2-benzyloxymethyl-4-methoxypyrrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,

N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,

N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,

N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrrolidin-1-ylmethyl)-
-2-(2-methylphenyl)benzoyl]methionine,

N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,

N-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine,

N-[4-(2-morpholin-4-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine,

N-[4-(2-(N-cyclohexyl-N-methylamino)methylpyrrolidin-1-ylmethyl)-2-(2-

- methylphenyl)benzoyl]methionine,
N-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
195 N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-[E-2-hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-
200 methylphenyl)benzoyl]methionine, lithium salt,
N-[4-[E-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)-
prop-2-enyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N--benzyloxy-N-butylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
205 N-[4-N--butyl-N-(3,5-difluorobenzyl)aminooxymethyl-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N--butyl-N-(cyclohexylmethoxy)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N--butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)-
210 benzoyl]methionine, lithium salt,
N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-
methionine,
215 N-[4-((cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-((cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-((cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-
220 methylphenyl)benzoyl]methionine,
N-[4-(di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)-
benzoyl]methionine,
225 N-[4-(di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-

methionine,

N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine, lithium salt.,

N-[4-(2-(2-cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,

N-[4-(2-(2-cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,

N-[4-(2-(2-cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt, and

N-[4-(4-cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt.

10. A compound selected from the group consisting of
 - [4-((2S,5S)-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine, hydrochloride,
 - [4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine,
 - (4-piperazinylmethyl-2-phenylbenzoyl)methionine,
 - [4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine,
 - [4-(5-cyclohexylmethyloxazolid-2-on-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
 - N-[4-(2-(2-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 - N-[4-(2-(2-phenoxyphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
 - N-[4-(2-(2-phenoxyphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
 - N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 - N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
 - N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 - N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 - N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,

lithium salt,
N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
N-[4-(2-(4-cyclohexylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
N-[4-(2-(fluoren-4-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(naphth-2-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(naphth-1-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(3-phenylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(3-naphth-2-ylpropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(3-cyclohexylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-phenylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(4-naphth-2-ylbut-4-on-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-naphth-2-ylbut-4-ol-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(4-cyclohexylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-cyclohexylbutyl)-2-(2-methylphenyl)benzoyl]methionine sodium salt,
N-[4-(5-phenylpent-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-pyrimidin-5-ylethynyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-pyrimidin-5-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,

N-[4-(2-pyrazin-2-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(3-naphth-2-ylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(2,3-diphenylpropan-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(N-benzyl-N-phenylaminosulfonyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-2-cyclohexylethylaminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-(1-benzylpiperidin-4-ylaminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-N-(2-piperidin-1-ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-N-(2-morpholin-1-ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-(2-(3,4-dimethoxyphenyl)ethylaminosulfonyl)-2-phenylbenzoyl]-
methionine, lithium salt,
N-[4-(3-(2-methylpiperidin-1-yl)propylaminosulfonyl)-2-phenylbenzoyl]-
methionine, lithium salt,
N-[4-iodo-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
N-[4-(2-(thiazol-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(2-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(3-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-phenylcyclohexylidenyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-syn-(4-phenylcyclohexylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-phenylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-(3-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,

N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(2-(3-phenoxy pyridazin-6-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(3-phenoxy pyridazin-6-yl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(2-benzyloxymethylpyrrolidin-1-yl)methyl)-2-(2-methylphenyl)benzoyl]methionine ,
N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2-(4-(2-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(4-(2-aminophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2-(4-(3-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(4-t-butoxycarbonylpiperazin-1-yl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(4-phenylpiperazin-1-yl)methyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-N-(1,3-diphenylpropan-2-yl)iminooxymethyl-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(N-hept-4-ylaminooxymethyl)-2-(2-methylphenyl)benzoyl]-methionine,

N-[4-(3-benzyloxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine ,
N-[4-(3-benzyloxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine ,
N-[4-(3-cyclohexylmethoxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine ,
N-[4-(2-phenoxyethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine ,
N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine ,
N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine ,
N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-benzylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(4-benzylpiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(4-cyclohexylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,

N-[4-(2(S)-cyclohexylmethoxymethylazetidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-morpholin-4-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(N-cyclohexyl-N-methylamino)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,

N-{4-[E-2-hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl}methionine, lithium salt,
N-{4-[E-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)-prop-2-enyl]-2-(2-methylphenyl)benzoyl}methionine, lithium salt,
N-[4-N-benzyloxy-N-butylaminomethyl-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-N-butyl-N-(3,5-difluorobenzyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-butyl-N-(cyclohexylmethoxy)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-((cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-((cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-((cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine, lithium salt.,
N-[4-(2-(2-cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(2-cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,

N-[4-(2-(2-cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt, and
N-[4-(4-cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt.

11. A method of inhibiting protein isoprenyl transferases in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
12. A composition for inhibiting protein isoprenyl transferases comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim 1.
13. A method for inhibiting or treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1 alone or in combination with another chemotherapeutic agent.
14. A composition for the treatment of cancer comprising a compound of claim 1 in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.
15. A method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
- 5 16. A composition for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both comprising a compound of claim 1 in combination with a pharmaceutical carrier.
- 5 17. A method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
18. A composition for treating or preventing restenosis in a mammal comprising a

compound of claim 1 in combination with a pharmaceutically acceptable carrier.

15. A method of inhibiting protein isoprenyl transferases in a mammal in need of , such treatment comprising administering to the mammal a therapeutically , effective amount of a compound of claim 1.
16. A composition for inhibiting protein isoprenyl transferases comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim 1.
17. A method for inhibiting or treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1 alone or in combination with another chemotherapeutic agent.
18. A composition for the treatment of cancer comprising a compound of claim 1 in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.
19. A method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
- 5 20. A composition for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both comprising a compound of claim 1 in combination with a pharmaceutical carrier.
- 5 21. A method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
22. A composition for treating or preventing restenosis in a mammal comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/09297

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database HCAPLUS on STN, 1997:247953, BOYLE, F.t. et al., 'Preparation of 2-aminomethyl-4-mercaptopyrrolidines and analogs as farnesyl transferase inhibitors', 20 February 1997, PCT Int. Appl. 189 pp., see entire abstract.	1-22
X	Database HCAPLUS on STN, 1996:567259, SEBTI et al., 'Peptidomimetic inhibitors of prenyl transferases, preparation and activity of the peptidomimetics, and use for treating tumors', 18 July 1996, PCT Int. Appl. 186 pp., see entire abstract.	1-22



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A document defining the general state of the art which is not considered to be of particular relevance	*X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E earlier document published on or after the international filing date	*Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*& document member of the same patent family
*O document referring to an oral disclosure, use, exhibition or other means	
*P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 SEPTEMBER 1998

Date of mailing of the international search report

19 OCT 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

YOGENDRA N. GUPTA

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/09297

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/38, 31/39, 31/40, 31/415, 31/42, 31/425, 31/44, 31/445, 31/495, 31/505, 31/095, 31/18; C07D 207/09, 233/54, 239/24, 241/04, 263/02, 277/28, 307/00, 333/00, 209/10; C07C 303/00, 307/00, 309/00, 313/00

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/255, 256, 331, 351, 357, 371, 400, 419, 423, 424, 439, 447, 461, 570, 604; 544/335, 400; 546/225, 300, 312, 336; 548/196, 338.1, 495, 543; 549/69, 76, 491; 564/42, 49

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/255, 256, 331, 351, 357, 371, 400, 419, 423, 424, 439, 447, 461, 570, 604; 544/335, 400; 546/225, 300, 312, 336; 548/196, 338.1, 495, 543; 549/69, 76, 491; 564/42, 49

ERROR: undefined
OFFENDING COMMAND:

STACK: